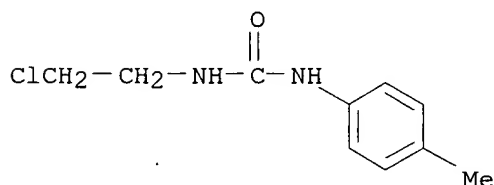
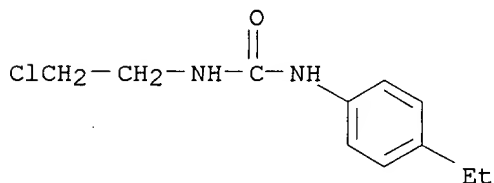


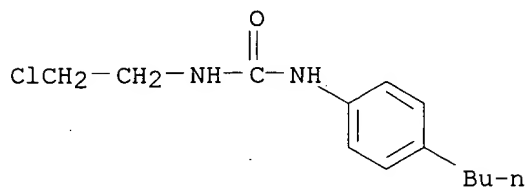
ACCESSION NUMBER: 1995:353302 CAPLUS
 DOCUMENT NUMBER: 122:239289
 TITLE: Synthesis and cytotoxic activity of new
 alkyl[3-(2-chloroethyl)ureido]benzene derivatives
 AUTHOR(S): Bechard, P.; Lacroix, J.; Poyet, P.; Gaudreault, R. C.
 CORPORATE SOURCE: Centre de recherche, Hopital Saint-Francois d'Assise,
 Quebec, G1L 3L5, Fr.
 SOURCE: Eur. J. Med. Chem. (1994), 29(12), 963-6
 CODEN: EJMCA5; ISSN: 0223-5234
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Several N-(2-chloroethyl)-N'-Ph urea derivs. [i.e., alkyl[3-(2-
 chloroethyl)ureido]benzene derivs.] were prepd. as potential anticancer
 agents. These compds. were prepd. from anilines and 2-
 chloroethylisocyanate. Their cytotoxic activity was evaluated on human
 breast **cancer** (MDA-MB-231), human colon adenocarcinoma (LoVo)
 and mouse lymphocytic leukemia (P388D1) tumor cell lines. Several new
 ureas were significantly more cytotoxic than the nitrogen mustard
 chlorambucil. The biol. activity of these arom. urea derivs. seems to be
 related to the nature and position of the alkyl substituents on the arom.
 ring. Substitution by branched alkyl groups on position 4 of the arom.
 ring led to cytotoxic mols. which are up to 5 times more potent than the
 std. chlorambucil.
 IT **15145-35-4P**, N-(2-Chloroethyl)-N'-(4-methylphenyl)urea
102433-48-7P, N-(2-Chloroethyl)-N'-(4-ethylphenyl)urea
113849-19-7P, N-(4-Butylphenyl)-N'-(2-Chloroethyl)urea
118202-58-7P, N-(2-Chloroethyl)-N'-(4-propylphenyl)urea
118202-59-8P, N-(2-Chloroethyl)-N'-[4-(1,1-
 dimethylethyl)phenyl]urea **161194-45-2P** **161194-47-4P**,
 N-(2-Chloroethyl)-N'-[4-(1-methylethyl)phenyl]urea
 RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic
 preparation); THU (Therapeutic use); BIOL (Biological study); PREP
 (Preparation); USES (Uses)
 (prepn. and cytotoxicity of N-(chloroethyl)-N'-Ph ureas)
 RN 15145-35-4 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-(4-methylphenyl)- (9CI) (CA INDEX NAME)



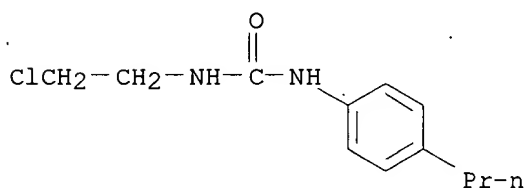
RN 102433-48-7 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-(4-ethylphenyl)- (9CI) (CA INDEX NAME)



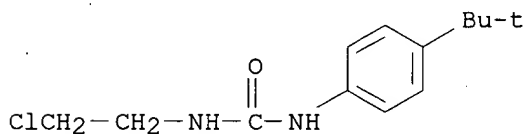
RN 113849-19-7 CAPLUS
CN Urea, N-(4-butylphenyl)-N'-(2-chloroethyl)- (9CI) (CA INDEX NAME)



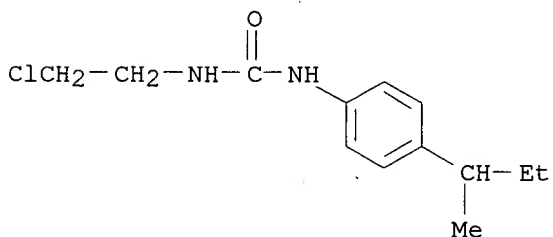
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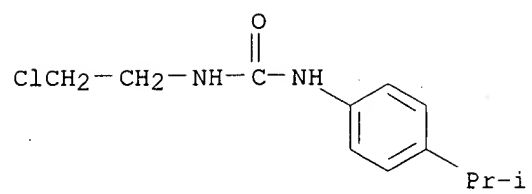
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CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



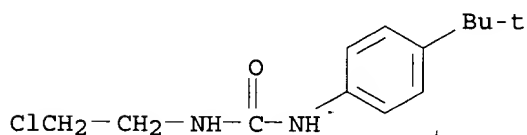
RN 161194-45-2 CAPLUS
CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CAPLUS
CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



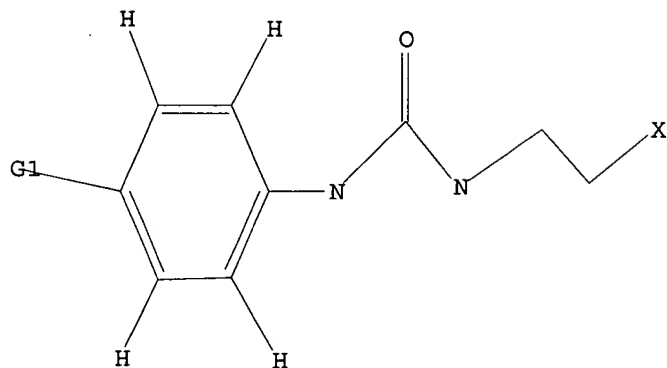
ACCESSION NUMBER: 1994:645277 CAPLUS
 DOCUMENT NUMBER: 121:245277
 TITLE: Lack of cross-resistance to a new cytotoxic
 arylchloroethyl urea in various **drug**
 -resistant tumor cells
 AUTHOR(S): Gaudreault, Rene C.; Alaoui-Jamali, Moulay A.; Batist,
 Gerald; Bechard, Philippe; Lacroix, Jacques; Poyet,
 Patrick
 CORPORATE SOURCE: Cent. de recherche, Hop. St. d'Assise, PQ, G1L 3L5,
 Can.
 SOURCE: Cancer Chemother. Pharmacol. (1994), 33(6), 489-92
 CODEN: CCPHDZ; ISSN: 0344-5704
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB 1-Aryl 3-(2-chloroethyl) ureas (CEUs), a new class of potent
 antineoplastic agents, were recently developed in our lab. These compds.
 were designed from the arom. moiety of chlorambucil and the unnitrosated
 pharmacophore of carmustine. In the present study we investigated the
 effect of the potent CEU deriv. 4-tert-butyl-[3-(2-chloroethyl)ureido]
 benzene (tBCEU) on tumor cell lines selected for resistance to a wide
 range of anticancer **drugs**. The resistance mechanisms found in
 these cells included increased expression of P-glycoprotein, increased
 intracellular concn. of glutathione and/or glutathione-S-transferase
 activity, alteration of topoisomerase II, and increased DNA repair.
 Whereas the resistant cell lines were found to be highly resistant to a
 panel of clin. known anticancer **drugs**, tBCEU was found to be
 equally cytotoxic to both resistant and parental cells. The
 nitrobenzylpyridine assay indicated that tBCEU is a weaker alkylating
 agent than chlorambucil. This lack of cross-resistance in various
 resistant tumor cells suggests that tBCEU could be potentially useful in
 the treatment of **cancers** resistant to conventional anticancer
drugs.
 IT 118202-59-8
 RL: BIOL (Biological study)
 (antitumor effect in various **drug**-resistant cells, lack of
 cross-resistance to)
 RN 118202-59-8 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX
 NAME)



=>
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L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



G1 Et,n-Pr,i-Pr,n-Bu,i-Bu,s-Bu,t-Bu

Structure attributes must be viewed using STN Express query preparation.

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SEARCH TIME: 00.00.01

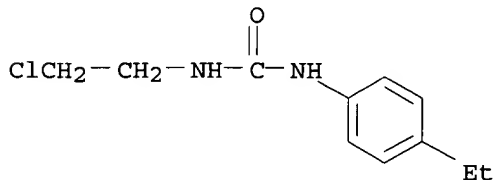
1 ANSWERS

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 2796 TO 4404
PROJECTED ANSWERS: 1 TO 80

L2 1 SEA SSS SAM L1

=> d scan

L2 1 ANSWERS REGISTRY COPYRIGHT 2001 ACS
IN Urea, N-(2-chloroethyl)-N'-(4-ethylphenyl)- (9CI)
MF C11 H15 Cl N2 O



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

=> s l1 full

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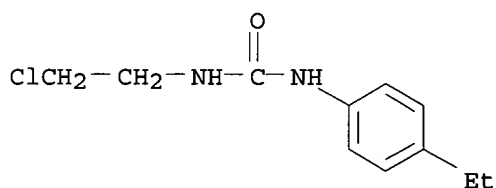
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SEARCH TIME: 00.00.03

13 ANSWERS

L3 13 SEA SSS FUL L1

=> d scan

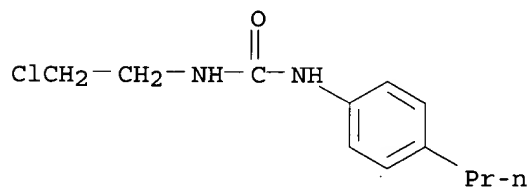
L3 13 ANSWERS REGISTRY COPYRIGHT 2001 ACS
IN Urea, N-(2-chloroethyl)-N'-(4-ethylphenyl)- (9CI)
MF C11 H15 Cl N2 O



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

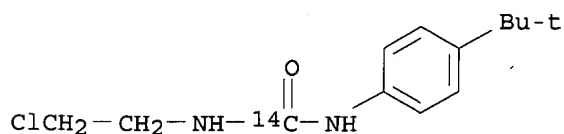
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):10

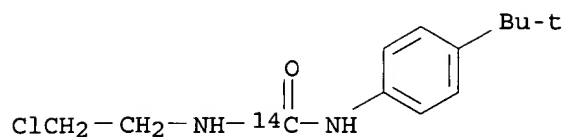
L3 13 ANSWERS REGISTRY COPYRIGHT 2001 ACS
IN Urea, N-(2-chloroethyl)-N'-(4-propylphenyl)- (9CI)
MF C12 H17 Cl N2 O



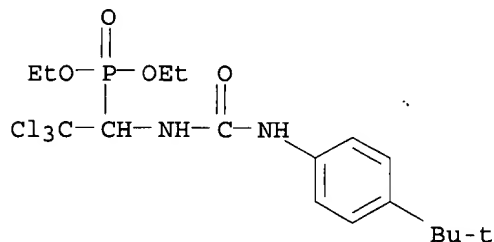
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 13 ANSWERS REGISTRY COPYRIGHT 2001 ACS
IN Urea-14C, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI)
MF C13 H19 Cl N2 O



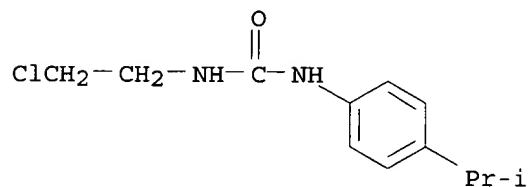


L3 13 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Phosphonic acid, [2,2,2-trichloro-1-[[[4-(1,1-dimethylethyl)phenyl]amino]carbonyl]amino]ethyl]-, diethyl ester (9CI)
 MF C17 H26 Cl3 N2 O4 P



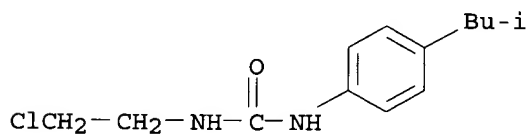
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 13 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI)
 MF C12 H17 Cl N2 O



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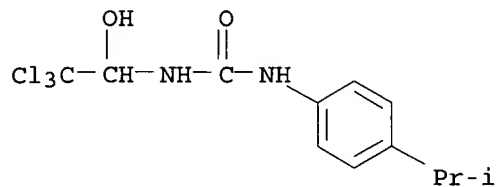
L3 13 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloroethyl)-N'-[4-(2-methylpropyl)phenyl]- (9CI)
 MF C13 H19 Cl N2 O



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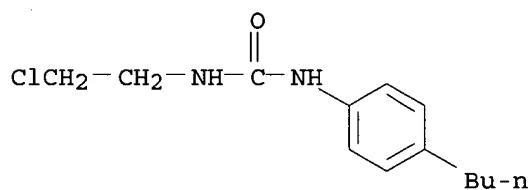
L3 13 ANSWERS REGISTRY COPYRIGHT 2001 ACS

IN Urea, N-[4-(1-methylethyl)phenyl]-N'-(2,2,2-trichloro-1-hydroxyethyl)-
(9CI)
MF C12 H15 Cl3 N2 O2



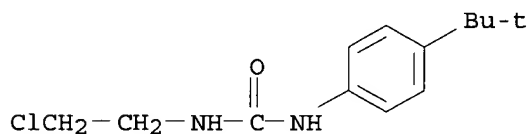
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 13 ANSWERS REGISTRY COPYRIGHT 2001 ACS
IN Urea, N-(4-butylphenyl)-N'-(2-chloroethyl)- (9CI)
MF C13 H19 Cl N2 O



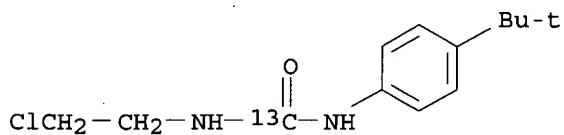
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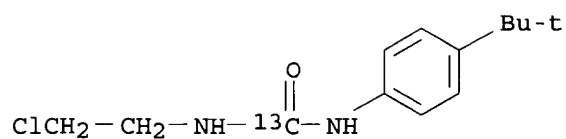
L3 13 ANSWERS REGISTRY COPYRIGHT 2001 ACS
IN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI)
MF C13 H19 Cl N2 O



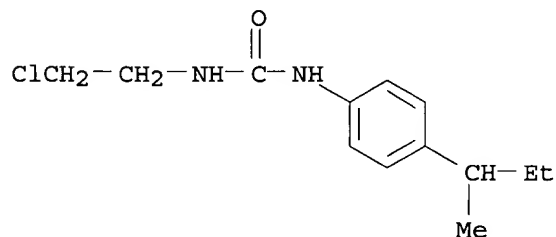
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 13 ANSWERS REGISTRY COPYRIGHT 2001 ACS
IN Urea-13C, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI)
MF C13 H19 Cl N2 O





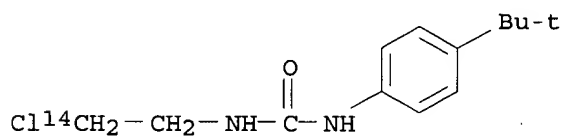
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 MF C13 H19 Cl N2 O



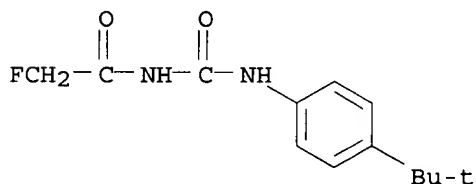
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):10

L3 13 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloroethyl-2-¹⁴C)-N'-(4-(1,1-dimethylethyl)phenyl)- (9CI)
 MF C13 H19 Cl N2 O



L3 13 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, 1-(p-tert-butylphenyl)-3-(fluoroacetyl)- (7CI, 8CI)
 MF C13 H17 F N2 O2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

DOCUMENT NUMBER: 138:138664
 TITLE: Solid golf balls with excellent repulsion and flying properties and hitting feel
 INVENTOR(S): Sakagami, Masatake; Mano, Satoshi
 PATENT ASSIGNEE(S): Sumitomo Rubber Industries Co., Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2003038682	A2	20030212	JP 2001-232512	20010731

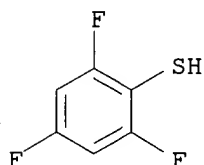
PRIORITY APPLN. INFO.: JP 2001-232512 20010731

AB The golf balls consist of .gtoreq.1 core layer and .gtoreq.1 cover layer, where .gtoreq.1 core layer is formed by vulcanizing rubber compns. contg. covulcanizers, org. peroxides, BaSO₄, and F-substituted thiophenols and/or their salts with mono- or bivalent metals. Thus, high-cis-butadiene rubber (JSR-BR 11) contg. Zn acrylate 30, ZnO 10, BaSO₄ 10.8, dicumyl peroxide 0.5, and pentafluorothiophenol 0.5 phr was kneaded and hot-pressed to give a core showing compression deflection 3.65 mm (under 98-127 N load) and repulsion coeff. 0.830 at low head speed (35 m/s) and 0.742 at high head speed (50 m/s).

IT **494197-28-3**
 RL: MOA (Modifier or additive use); USES (Uses)
 (solid golf balls with good repulsion and flying properties and hitting feel)

RN 494197-28-3 CAPLUS

CN Benzenethiol, 2,4,6-trifluoro-, magnesium salt (9CI) (CA INDEX NAME)



1/2 Mg

L33 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:416955 CAPLUS

DOCUMENT NUMBER: 135:19874

TITLE: Preparation of N6- heterocyclic 5'-thio substituted adenosine derivatives as partial or full A1 receptor agonists

INVENTOR(S): Zablocki, Jeff A.; Palle, Venkata P.; Varkhedkar, Vaibhav; Belardinelli, Luiz

PATENT ASSIGNEE(S): CV Therapeutics, Inc., USA

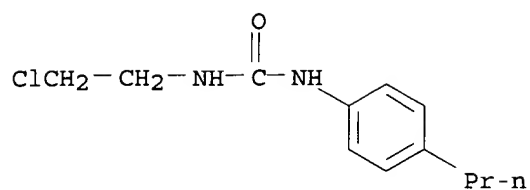
SOURCE: PCT Int. Appl., 57 pp.
 CODEN: PIXXD2

DOCUMENT TYPE: Patent

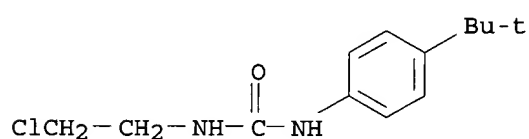
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 6

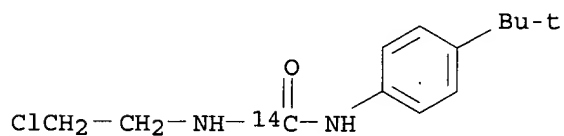
PATENT INFORMATION:



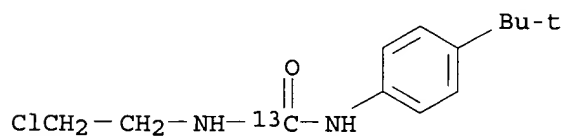
L5 12 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl] - (9CI)
 MF C13 H19 Cl N2 O



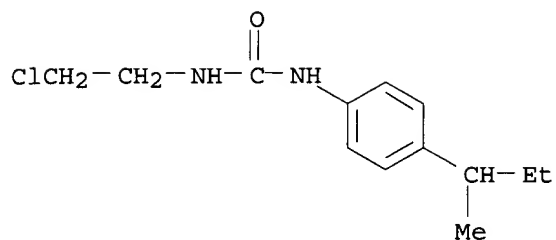
L5 12 ANSWERS REGISTRY COPYRIGHT 2001 ACS
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 MF C13 H19 Cl N2 O



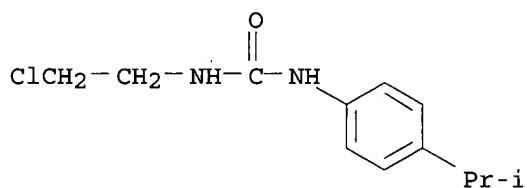
L5 12 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea-14C, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl] - (9CI)
 MF C13 H19 Cl N2 O



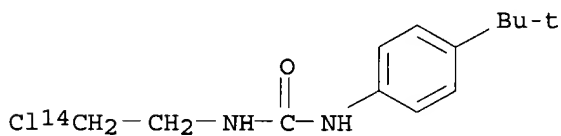
L5 12 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl] - (9CI)
 MF C13 H19 Cl N2 O



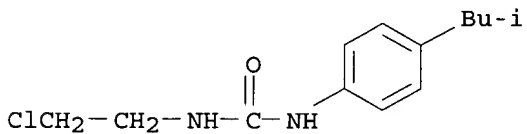
L5 12 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl] - (9CI)
 MF C12 H17 Cl N2 O



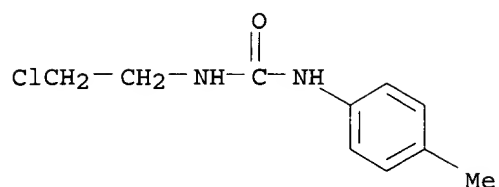
L5 12 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloroethyl-2-14C)-N'-[4-(1,1-dimethylethyl)phenyl] - (9CI)
 MF C13 H19 Cl N2 O



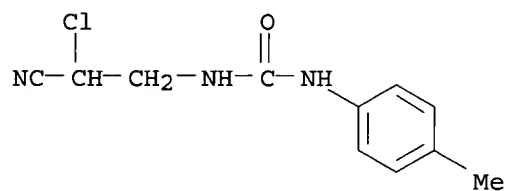
L5 12 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloroethyl)-N'-[4-(2-methylpropyl)phenyl] - (9CI)
 MF C13 H19 Cl N2 O



L5 12 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloroethyl)-N'-(4-methylphenyl) - (9CI)
 MF C10 H13 Cl N2 O

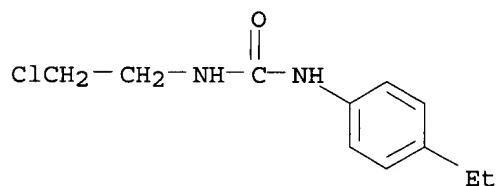


L5 12 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloro-2-cyanoethyl)-N'-(4-methylphenyl)- (9CI)
 MF C11 H12 Cl N3 O



HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):10

L5 12 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloroethyl)-N'-(4-ethylphenyl)- (9CI)
 MF C11 H15 Cl N2 O



ALL ANSWERS HAVE BEEN SCANNED

=> s l5 and 1/n
 3588181 1/N
 L6 0 L5 AND 1/N

=> s l5 and 2/n
 3383695 2/N
 L7 11 L5 AND 2/N

=> file caplus
 COST IN U.S. DOLLARS

FULL ESTIMATED COST

SINCE FILE	TOTAL
ENTRY	SESSION
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FILE COVERS 1947 - 19 Sep 2001 VOL 135 ISS 13
FILE LAST UPDATED: 18 Sep 2001 (20010918/ED)

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=> s l7

L8 16 L7

=> s l8 and (pharmaceutical or prodrug or drug or medicament or cancer or tubulin)

148488 PHARMACEUTICAL
66713 PHARMACEUTICALS
187047 PHARMACEUTICAL
(PHARMACEUTICAL OR PHARMACEUTICALS)
6496 PRODRUG
5308 PRODRUGS
8273 PRODRUG
(PRODRUG OR PRODRUGS)
396792 DRUG
229754 DRUGS
518909 DRUG
(DRUG OR DRUGS)
2228 MEDICAMENT
2148 MEDICAMENTS
4074 MEDICAMENT
(MEDICAMENT OR MEDICAMENTS)
143439 CANCER
19662 CANCERS
149254 CANCER
(CANCER OR CANCERS)
10593 TUBULIN
7626 TUBULINS
11377 TUBULIN
(TUBULIN OR TUBULINS)

L9 10 L8 AND (PHARMACEUTICAL OR PRODRUG OR DRUG OR MEDICAMENT OR CANCER OR TUBULIN)

=> d ibib abs hitstr 1-10

L9 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:489217 CAPLUS

DOCUMENT NUMBER: 135:71264

TITLE: Carbamidobenzenes for use as antitumor .beta.-
tubulin inhibitors

INVENTOR(S): Gaudreault, Rene C.; Legault, Jean

PATENT ASSIGNEE(S): Universite Laval, Can.

SOURCE: PCT Int. Appl., 43 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047504	A2	20010705	WO 2000-CA1579	20001222
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: US 1999-171615 P 19991223

AB Disclosed herein are benzene carbamide .beta.-**tubulin** inhibitors, **prodrugs** thereof, and therapeutically acceptable salts thereof for use as anti-**cancer** cell proliferation agents.

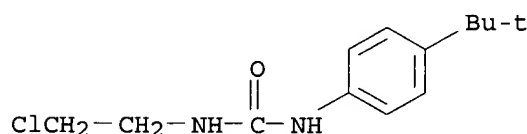
IT **118202-59-8 161194-45-2 161194-47-4**

RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(carbamidobenzenes for use as antitumor .beta.-**tubulin** inhibitors)

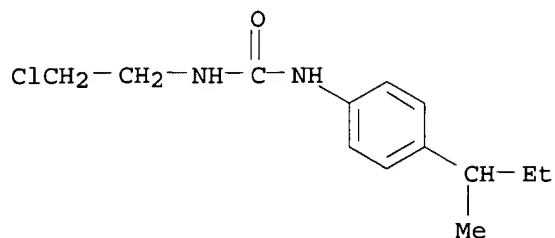
RN 118202-59-8 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)

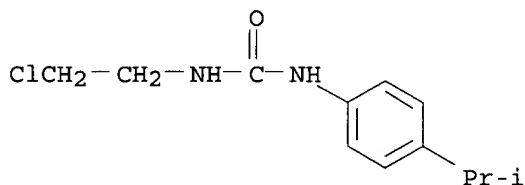


RN 161194-45-2 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



L9 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:55542 CAPLUS

DOCUMENT NUMBER: 134:246870

TITLE: Antimitotic antitumor agents: synthesis, structure-activity relationships, and biological characterization of N-aryl-N'-(2-chloroethyl)ureas as new selective alkylating agents

AUTHOR(S): Mounetou, Emmanuelle; Legault, Jean; Lacroix, Jacques; C-Gaudreault, Rene

CORPORATE SOURCE: Centre de Recherche, CHUQ Hopital Saint-Francois d'Assise, QC, G1L3L5, Can.

SOURCE: J. Med. Chem. (2001), 44(5), 694-702

CODEN: JMCMAR; ISSN: 0022-2623.

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A series of N-aryl-N'-(2-chloroethyl) ureas (CEUs) and derivs. were synthesized and evaluated for antiproliferative activity against a wide panel of tumor cell lines. Systematic structure-activity relationship (SAR) studies indicated that: (i) a branched alkyl chain or a halogen at the 4-position of the Ph ring or a fluorenyl/indanyl group, (ii) an exocyclic urea function, and (iii) a N'-2-chloroethyl moiety were required to ensure significant cytotoxicity. Biol. expts., such as immunofluorescence microscopy, confirmed that these promising compds. alter the cytoskeleton by inducing microtubule depolymn. via selective alkylation of .beta.-tubulin. Subsequent evaluations demonstrated that potent CEUs were weak alkylators, were non-DNA-damaging agents, and did not interact with the thiol function of either glutathione or glutathione reductase. Therefore, CEUs are part of a new class of antimitotic agents. Finally, among the series of CEUs evaluated, compds. N' 4-isopropylphenyl, 4-sec-butylphenyl, 4-tert-butylphenyl, and 4-iodophenyl N-(2-chloroethyl)ureas were selected for further in vivo trials.

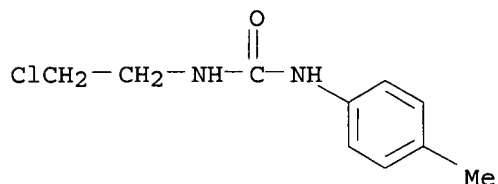
IT 15145-35-4 102433-48-7 113849-19-7
 118202-58-7 118202-59-8 161194-45-2
 161194-47-4 331171-31-4

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(synthesis, SAR, and biol. characterization of arylchloroethyl ureas as new selective alkylating agents)

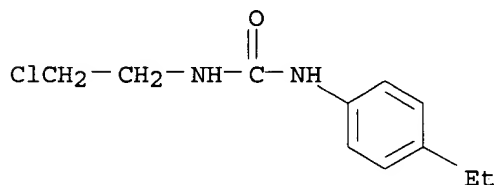
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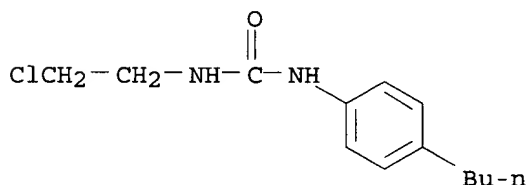
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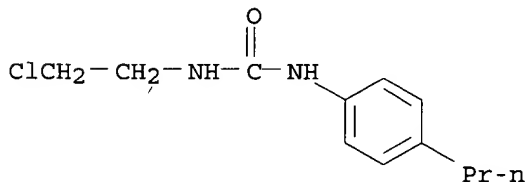
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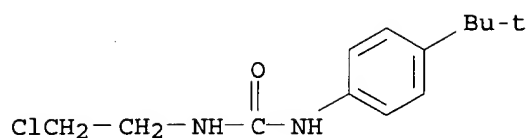
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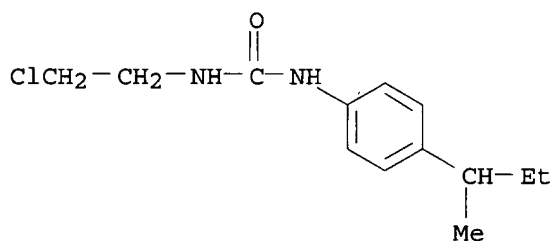


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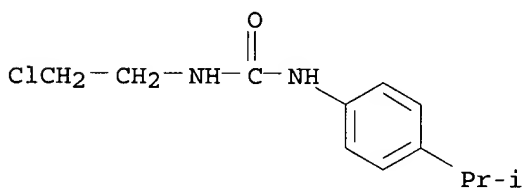
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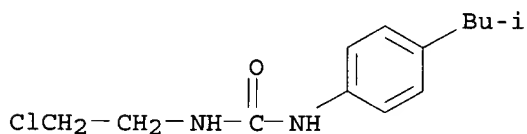
RN 161194-45-2 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 331171-31-4 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(2-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT:

REFERENCE(S):

22

- (1) Bardos, T; J Med Chem 1965, V8, P167 CAPLUS
 - (2) Becker, K; Methods Enzymol 1995, V251, P173 CAPLUS
 - (4) Cohen, M; Biochem Pharmacol 1988, V37, P3317 CAPLUS
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 - (6) Frischer, H; J Clin Invest 1993, V92, P2761 CAPLUS
- ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:160216 CAPLUS

DOCUMENT NUMBER: 132:302978

TITLE: Microtubule disruption induced in vivo by alkylation of .beta.-**tubulin** by 1-aryl-3-(2-chloroethyl)ureas, a novel class of soft alkylating agents

AUTHOR(S): Legault, Jean; Gaulin, Jean-Francois; Mounetou, Emmanuelle; Bolduc, Sebastien; Lacroix, Jacques; Poyet, Patrick; Gaudreault, Rene C.

CORPORATE SOURCE: Biotechnology Unit, Biomaterial Institute of Quebec, Centre Hospitalier Universitaire de Quebec, Laval University, Quebec City, PQ, G1L 3L5, Can.

SOURCE: Cancer Res. (2000), 60(4), 985-992

CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: AACR Subscription Office

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have previously reported that 4-tert-butyl-[3-(2-chloroethyl)ureido] benzene (4-tBCEU), a potent cytotoxic agent, modulates the synthesis of **tubulins**, suggesting that its cytotoxicity may be mediated through an antimicrotubule mechanism. Indeed, 4-t-BCEU and its 4-iso-Pr (4-iso-Pr [3-(2-chloroethyl)ureido] benzene) and 4-sec-Bu (4-sec-Bu [3-(2-chloroethyl)ureido] benzene) homologues induced disruption of the cytoskeleton and arrest of the cell cycle in G2 transition and mitosis. To better understand the mechanisms responsible for microtubule disruption by 1-aryl-3-(2-chloroethyl)ureas (CEU), we first examd. their cytotoxicity on Chinese hamster ovary cells resistant to vinblastine and colchicine due to the expression of mutated **tubulins** (CHO-VV 3-2). These cells showed resistance to CEU, e.g., 4-tBCEU having an IC50 of 21.3 +/- 1.1 .mu.M as compared with an IC50 of 11.6 +/- 0.7 .mu.M for wild-type cells, suggesting a direct effect of the **drugs** on **tubulins**. Western blot anal. confirmed the disruption of microtubules and evidenced the formation of an addnl. immunoreactive .beta.-**tubulin** with an apparent lower mol. wt. on SDS polyacrylamide gel. Incubation of MDA-MB-231 cells with [urea-14C]-4-tBCEU revealed the presence of a radioactive protein that coincided with the addnl. .beta.-**tubulin** band, indicating that CEU could covalently bind to the .beta.-**tubulin**. The 4-tBCEU-binding site on .beta.-**tubulin** was identified by competition of the CEU with colchicine, vinblastine, and iodoacetamide, a specific alkylating agent of sulfhydryl groups of cysteine residues. Colchicine, but not vinblastine, prevented the formation of the addnl. .beta.-**tubulin** band, suggesting that 4-tBCEU alkylates either Cys239 or Cys354 residues near the colchicine-binding site. To det. the cysteine residue alkylated by 4-tBCEU, we incubated the radiolabeled **drug** with human neuroblastoma cells (SK-N-SH) that overexpress the .beta.III-**tubulin**, an isoform where Cys239 is replaced by a serine residue. The results clearly showed that .beta.III-**tubulin** is not alkylated by [urea-14C]-4-tBCEU, suggesting that cysteine 239 residue is essential for the reactivity of 4-tBCEU with .beta.-**tubulin**. Taken together, these findings indicate that the mechanism of cytotoxicity of CEU involves microtubule depolymn. through alkylation of .beta.-**tubulin**.

IT 102433-48-7 113849-19-7 118202-59-8

161194-45-2 161194-47-4

RL: BAC (Biological activity or effector, except adverse); THU

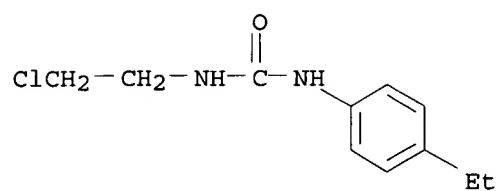
(Therapeutic use); BIOL (Biological study); USES (Uses)

(microtubule disruption induced by .beta.-**tubulin** alkylation

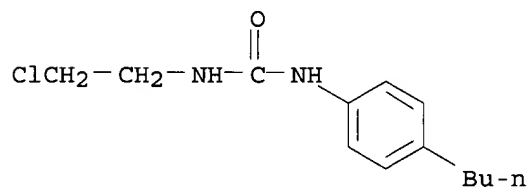
by 1-aryl-3-(2-chloroethyl)ureas, novel class of soft alkylating agents)

RN 102433-48-7 CAPLUS

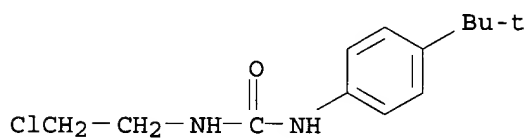
CN Urea, N-(2-chloroethyl)-N'-(4-ethylphenyl)- (9CI) (CA INDEX NAME)



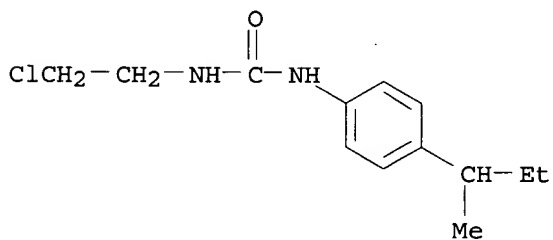
RN 113849-19-7 CAPLUS
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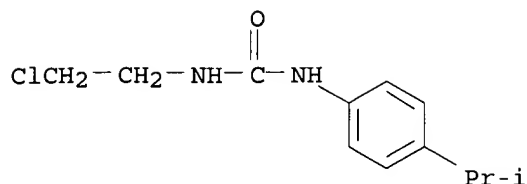
RN 118202-59-8 CAPLUS
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RN 161194-45-2 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



L9 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:51302 CAPLUS

DOCUMENT NUMBER: 130:204670

TITLE: Interaction between lipid bilayers and a new class of antineoplastic agents derived from

arylchloroethylurea: a 2H solid-state NMR study
 AUTHOR(S): Saint-Laurent, Audrey; Boudreau, Nadine; Gaudreault, Rene C.-; Poyet, Patrick; Auger, Michele

CORPORATE SOURCE: Departement de chimie, Centre de recherche en sciences et ingenierie des macromolecules, Universite Laval, Quebec, PQ, G1K 7P4, Can.

SOURCE: Biochem. Cell Biol. (1998), 76(2/3), 465-471

CODEN: BCBIEQ; ISSN: 0829-8211

PUBLISHER: National Research Council of Canada

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have investigated the interaction between a new class of antineoplastic agents derived from arylchloroethylurea (CEU) and model membrane of dimyristoylphosphatidylcholine by deuterium NMR spectroscopy. The results indicate that the **drug** incorporates in the bilayer and causes an increase of the lipid acyl chain order, this effect being greater close to the interfacial region of the lipid bilayer. The increase in ordering is dependent on the nature (degree of ramification, length of the alkyl chain, and presence of a sulfur atom) as well as on the position of the R substituent and is correlated with the cytotoxicity of the **drugs**. More specifically, the more cytotoxic **drugs**, such as 4-sec-Bu CEU, are those having a bulky ramified substituent and those for which the ordering effect on the lipid bilayer is the smallest. On the other hand, the ordering effect is greater and seen all along the lipid acyl chains for the long-chain CEUs, such as n-hexadecyl CEU, which have been shown to have very weak cytotoxic activity. Finally, the results obtained as a function of the **drug** concn. indicate that the ordering effect is seen for lipid to **drug** molar ratios as low as 20:1.

IT 113849-19-7 161194-45-2 161194-47-4

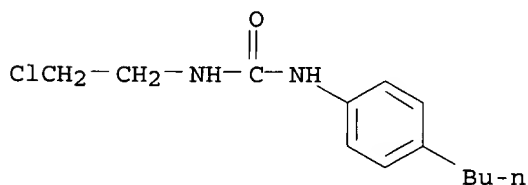
RL: BAC (Biological activity or effector, except adverse); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)

(interaction between lipid bilayers and antineoplastic agents derived from arylchloroethylurea, a 2H solid-state NMR study)

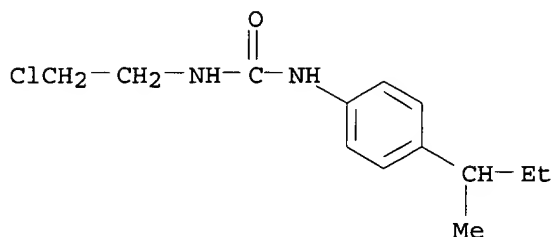
RN 113849-19-7 CAPLUS

CN Urea, N-(4-butylphenyl)-N'-(2-chloroethyl)- (9CI) (CA INDEX NAME)

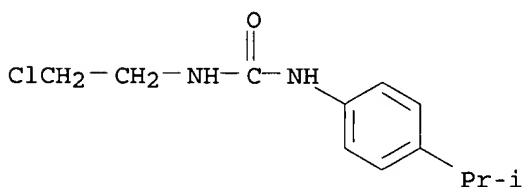


RN 161194-45-2 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CAPLUS
CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 21
REFERENCE(S): (1) Auger, M; Biochemistry 1988, V27, P4660 CAPLUS
(3) Bloom, M; Chem Phys Lett 1981, V80, P198 CAPLUS
(4) Bouchard, M; Biochim Biophys Acta 1996, V1282, P233 CAPLUS
(5) Davis, J; Biochim Biophys Acta 1983, V737, P117 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:129113 CAPLUS

DOCUMENT NUMBER: 128:252464

TITLE: Disposition and metabolism of a novel antineoplastic agent, 4-tert-butyl-[3-(2-chloroethyl)ureido]benzene, in mice

AUTHOR(S): Maurizis, Jean-Claude; Rapp, Maryse; Azim, El Mostafa; Gaudreault, Rene C.; Veyre, Annie; Madelmont, Jean-Claude

CORPORATE SOURCE: INSERM U 71, Clermont-Ferrand, 63005, Fr.

SOURCE: Drug Metab. Dispos. (1998), 26(2), 146-151

CODEN: DMDSAI; ISSN: 0090-9556

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 1-Aryl-3-(2-chloroethyl)ureas are new agents that have shown promising cytotoxic and antineoplastic activities. In this work, we studied the disposition and metab. of one of these mols., 4-tert-butyl-[3-(2-chloroethyl)ureido]benzene (tBCEU). tBCEU was labeled with ¹⁴C and ¹³C in the urea function and in the chloroethyl moiety. After i.p. administration of the mol. labeled in the urea function, radioactivity was widely distributed in the whole organism, including the brain. HPLC anal. of plasma showed that tBCEU was extensively metabolized, with <20% being

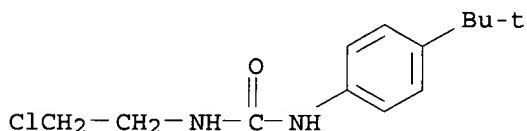
found in the plasma as unchanged tBCEU 1 h after administration. One main metabolite was identified by NMR and MS anal. as N-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]urea, widely conjugated to glucuronic acid. The same metabolite was found in the urine. After administration of tBCEU labeled in the chloroethyl moiety, the same tissue affinities were obsd., but the decrease of total radioactivity in blood and tissues was slower than that obsd. for the mol. labeled in the urea function. HPLC anal. of urine showed the presence of two main metabolites, identified by MS as thiodiacetic acid and its sulfoxide. From these results, we can deduce that the metabolic pathway of tBCEU involves N-dealkylation of the urea portion of the mol. and hydroxylation of the tert-Bu group. The strong cytochrome P 450 reactivity of the carbon adjacent to the urea portion of tBCEU is probably related to particular sensitivity to oxidn. at this position, based on the chem. structure of tBCEU. These results can explain the fact that the cytotoxic effect of tBCEU is not due to DNA alkylation, in contrast to that of its parent mol., chloroethylnitrosourea.

IT 118202-59-8

RL: BPR (Biological process); BIOL (Biological study); PROC (Process) (disposition and metab. of antineoplastic agent, 4-tert-butyl-[3-(2-chloroethyl)ureido]benzene, in mice)

RN 118202-59-8 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



L9 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1996:620540 CAPLUS

DOCUMENT NUMBER: 125:265268

TITLE: Interaction of antineoplastic drug 4-tert-butyl-[3-(2-chloroethyl) ureido] benzene with phosphatidylcholine bilayers: a differential scanning calorimetry and infrared spectroscopy study

AUTHOR(S): Gicquaud, Claude; Auger, Michele; Wong, Patrick T. T.; Poyet, Patrick; Boudreau, Nadine; C-Gaudreault, Rene
CORPORATE SOURCE: Dep. Chimie-Biologie, Univ. du Quebec, Trois-Rivieres, PQ, G9A 5H7, Can.

SOURCE: Arch. Biochem. Biophys. (1996), 334(2), 193-199
CODEN: ABBIA4; ISSN: 0003-9861

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have investigated the interaction between a new antineoplastic drug, 4-tert-butyl-[3-(2-chloroethyl)ureido] benzene (tBCEU), and distearoylphosphatidylcholine bilayers using differential scanning calorimetry, Fourier transform IR spectroscopy (FT-IR), and high-pressure IR spectroscopy. The results obtained with the three different techniques indicate that the drug incorporates in the lipid bilayer. More specifically, the incorporation of the tBCEU results in a decrease in the phase transition temp. of the lipid and in an increase in the amt. of gauche conformers in the liq.-cryst. phase. In the gel phase, high-pressure FT-IR results indicate that the incorporation of tBCEU decreases the acyl chain packing. In addn., the results suggest the presence of hydrogen bonding between the lipid carbonyl group and an hydrogen bond donor in the tBCEU mol. A possible candidate for this donor is NH group adjacent to the Ph ring. A model is proposed for the

incorporation of tBCEU in lipid bilayers, with the hydrophobic portion of the **drug** intercalated between the lipid bilayers and the hydrophilic region located close to the interfacial region of the bilayer.

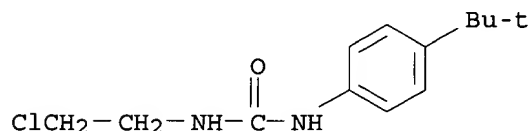
IT 118202-59-8

RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(interaction of antineoplastic **drug** 4-tert-butyl-[3-(2-chloroethyl) ureido] benzene with phosphatidylcholine bilayers: a differential scanning calorimetry and IR spectroscopy study)

RN 118202-59-8 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



L9 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1995:380362 CAPLUS

DOCUMENT NUMBER: 122:239336

TITLE: Preparation of arylurea derivatives and analogs as anticancer agents

INVENTOR(S): C.-Gaudreault, Rene; Poyet, Patrick

PATENT ASSIGNEE(S): Universite Laval, Can.

SOURCE: Can. Pat. Appl., 25 pp.

CODEN: CPXXEB

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2116621	AA	19940904	CA 1994-2116621	19940228
US 5530026	A	19960625	US 1995-369584	19950106
US 5750547	A	19980512	US 1996-664233	19960607

PRIORITY APPLN. INFO.: US 1993-25848 19930303

US 1995-369584 19950106

OTHER SOURCE(S): MARPAT 122:239336

AB Title compds. BACONHCH₂CH₂Cl (I; A = O, NH; B = Ph, indane, fluorene, indazole, indole, and pyridine, optionally substituted, **prodrug**, with provisos), are prepd,. I have antineoplastic activity without systemic toxicity and mutagenicity. To 4-sec-butylaniline in Et₂O was added 2-chloroethyl isocyanate to give I (B = 4-(EtCHMe)C₆H₄, A = NH). Anticancer activity was demonstrated.

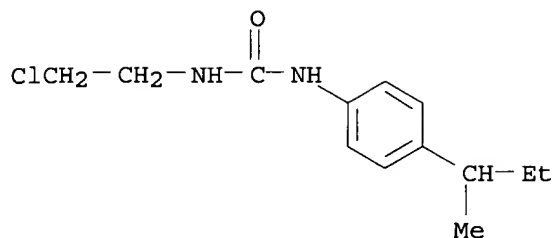
IT 161194-45-2P 161194-47-4P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

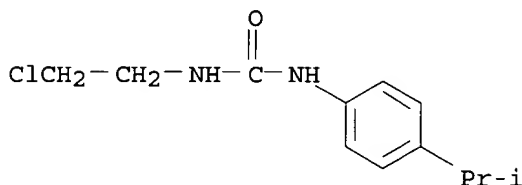
(prepn. of arylurea derivs. and analogs as anticancer agents)

RN 161194-45-2 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)

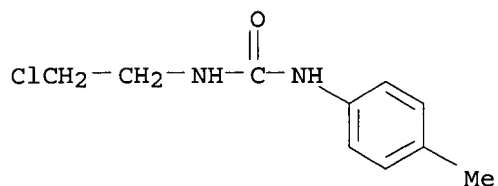


RN 161194-47-4 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



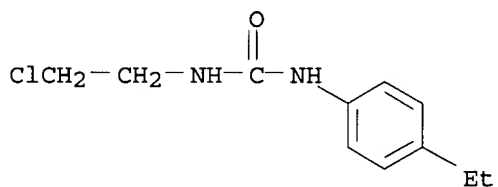
L9 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2001 ACS
 ACCESSION NUMBER: 1995:353302 CAPLUS
 DOCUMENT NUMBER: 122:239289
 TITLE: Synthesis and cytotoxic activity of new alkyl[3-(2-chloroethyl)ureido]benzene derivatives
 AUTHOR(S): Bechard, P.; Lacroix, J.; Poyet, P.; Gaudreault, R. C.
 CORPORATE SOURCE: Centre de recherche, Hopital Saint-Francois d'Assise, Quebec, G1L 3L5, Fr.
 SOURCE: Eur. J. Med. Chem. (1994), 29(12), 963-6
 CODEN: EJMCA5; ISSN: 0223-5234
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Several N-(2-chloroethyl)-N'-Ph urea derivs. [i.e., alkyl[3-(2-chloroethyl)ureido]benzene derivs.] were prepd. as potential anticancer agents. These compds. were prepd. from anilines and 2-chloroethylisocyanate. Their cytotoxic activity was evaluated on human breast **cancer** (MDA-MB-231), human colon adenocarcinoma (LoVo) and mouse lymphocytic leukemia (P388D1) tumor cell lines. Several new ureas were significantly more cytotoxic than the nitrogen mustard chlorambucil. The biol. activity of these arom. urea derivs. seems to be related to the nature and position of the alkyl substituents on the arom. ring. Substitution by branched alkyl groups on position 4 of the arom. ring led to cytotoxic mols. which are up to 5 times more potent than the std. chlorambucil.
 IT 15145-35-4P, N-(2-Chloroethyl)-N'-(4-methylphenyl)urea
 102433-48-7P, N-(2-Chloroethyl)-N'-(4-ethylphenyl)urea
 113849-19-7P, N-(4-Butylphenyl)-N'-(2-Chloroethyl)urea
 118202-58-7P, N-(2-Chloroethyl)-N'-(4-propylphenyl)urea
 118202-59-8P, N-(2-Chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]urea 161194-45-2P 161194-47-4P,
 N-(2-Chloroethyl)-N'-[4-(1-methylethyl)phenyl]urea
 RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. and cytotoxicity of N-(chloroethyl)-N'-Ph ureas)
 RN 15145-35-4 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-(4-methylphenyl)- (9CI) (CA INDEX NAME)



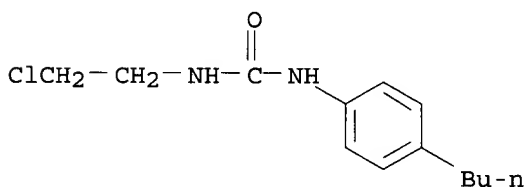
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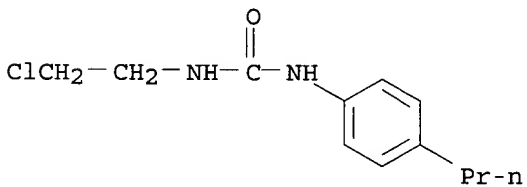
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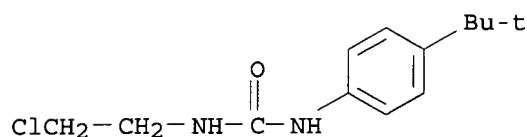
RN 118202-58-7 CAPLUS

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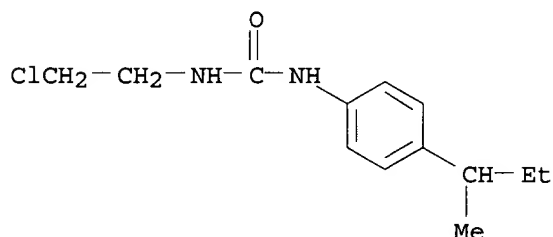


RN 118202-59-8 CAPLUS

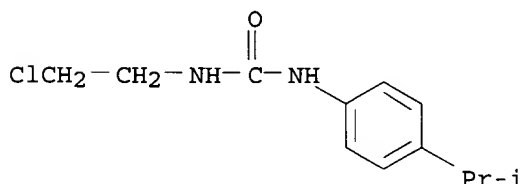
CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-45-2 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



L9 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2001 ACS
 ACCESSION NUMBER: 1994:645277 CAPLUS
 DOCUMENT NUMBER: 121:245277
 TITLE: Lack of cross-resistance to a new cytotoxic arylchloroethyl urea in various **drug**-resistant tumor cells
 AUTHOR(S): Gaudreault, Rene C.; Alaoui-Jamali, Moulay A.; Batist, Gerald; Bechard, Philippe; Lacroix, Jacques; Poyet, Patrick
 CORPORATE SOURCE: Cent. de recherche, Hop. St. d'Assise, PQ, G1L 3L5, Can.
 SOURCE: Cancer Chemother. Pharmacol. (1994), 33(6), 489-92
 CODEN: CCPHDZ; ISSN: 0344-5704
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB 1-Aryl 3-(2-chloroethyl) ureas (CEUs), a new class of potent antineoplastic agents, were recently developed in our lab. These compds. were designed from the arom. moiety of chlorambucil and the unnitrosated pharmacophore of carmustine. In the present study we investigated the effect of the potent CEU deriv. 4-tert-butyl-[3-(2-chloroethyl)ureido]benzene (tBCEU) on tumor cell lines selected for resistance to a wide range of anticancer **drugs**. The resistance mechanisms found in these cells included increased expression of P-glycoprotein, increased

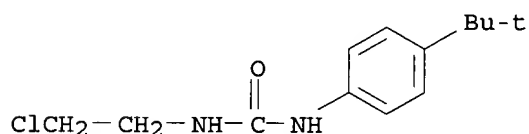
intracellular concn. of glutathione and/or glutathione-S-transferase activity, alteration of topoisomerase II, and increased DNA repair. Whereas the resistant cell lines were found to be highly resistant to a panel of clin. known anticancer **drugs**, tBCEU was found to be equally cytotoxic to both resistant and parental cells. The nitrobenzylpyridine assay indicated that tBCEU is a weaker alkylating agent than chlorambucil. This lack of cross-resistance in various resistant tumor cells suggests that tBCEU could be potentially useful in the treatment of **cancers** resistant to conventional anticancer **drugs**.

IT 118202-59-8

RL: BIOL (Biological study)
(antitumor effect in various **drug**-resistant cells, lack of cross-resistance to)

RN 118202-59-8 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



L9 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1994:400339 CAPLUS

DOCUMENT NUMBER: 121:339

TITLE: Effect of an aryl chloroethyl urea on **tubulin** and vimentin syntheses in a human breast **cancer** cell line

AUTHOR(S): Poyet, Patrick; Ritchot, Nathalie; Bechard, Philippe; Gaudreault, Rene C.

CORPORATE SOURCE: Cent. Rech., Hop. Saint - Francois d'Assise, Quebec, PQ, G1L 3L5, Can.

SOURCE: Anticancer Res. (1993), 13(5A), 1447-52
CODEN: ANTRD4; ISSN: 0250-7005

DOCUMENT TYPE: Journal

LANGUAGE: English

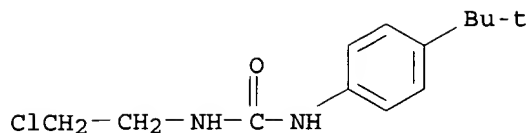
AB A new class of antineoplastic agents, 1-aryl-3-(2-chloroethyl)ureas (CEUs), was recently developed in the authors' lab. To optimize the pharmacol. and the biol. properties of this new class of compds. and to det. its mechanism of action, at the cellular level, the authors studied the effect of 4-tert-Bu-[3-(2-chloroethyl)ureido]benzene (tBCEU) on MDA-MB-231, a human breast **cancer** hormone-independent cell line. The effect of tBCEU on protein synthesis and on the accumulation of specific mRNAs was evaluated. The results indicate that tBCEU increases the synthesis of at least two proteins present in the cytoskeleton: **tubulin** and vimentin. The effect of tBCEU on their transcripts indicates that tBCEU decreases the accumulation of **tubulin** and vimentin mRNA. These results suggest that the antineoplastic activity of tBCEU is in part related to an alteration in the synthesis pathway of **tubulin** and vimentin.

IT 118202-59-8

RL: BIOL (Biological study)
(**tubulin** and vimentin formation inhibition by, in human breast **cancer** cell line, antitumor mechanism in relation to)

RN 118202-59-8 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



=> file medline

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
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FULL ESTIMATED COST	56.10	210.65
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
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CA SUBSCRIBER PRICE	-5.88	-5.88

FILE 'MEDLINE' ENTERED AT 17:31:51 ON 19 SEP 2001

FILE LAST UPDATED: 19 SEP 2001 (20010919/UP). FILE COVERS 1958 TO DATE.

On April 22, 2001, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE now contains IN-PROCESS records. See HELP CONTENT for details.

MEDLINE is now updated 4 times per week. A new current-awareness alert frequency (EVERYUPDATE) is available. See HELP UPDATE for more information.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2001 vocabulary. Enter HELP THESAURUS for details.

The OLDMEDLINE file segment now contains data from 1958 through 1965. Enter HELP CONTENT for details.

Left, right, and simultaneous left and right truncation are available in the Basic Index. See HELP SFIELDS for details.

THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE SUBSTANCE IDENTIFICATION.

=> d his

(FILE 'HOME' ENTERED AT 17:16:32 ON 19 SEP 2001)

FILE 'REGISTRY' ENTERED AT 17:19:32 ON 19 SEP 2001

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L2      2 S L1
L3      28 S L2 FULL
L4      14 S L3 AND (1/O AND 1/X)
L5      12 S L4 AND 1/NR
L6      0 S L5 AND 1/N
L7      11 S L5 AND 2/N

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FILE 'CAPLUS' ENTERED AT 17:22:38 ON 19 SEP 2001

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L8      16 S L7
L9      10 S L8 AND (PHARMACEUTICAL OR PRODRUG OR DRUG OR MEDICAMENT OR CA

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FILE 'MEDLINE' ENTERED AT 17:31:51 ON 19 SEP 2001

=> s l7

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L10     4 L7

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=> d all

L10 ANSWER 1 OF 4 MEDLINE
AN 1998122823 MEDLINE
DN 98122823 PubMed ID: 9456301
TI Disposition and metabolism of a novel antineoplastic agent,
4-tert-butyl-[3-(2-chloroethyl)ureido]benzene, in mice.
AU Maurizis J C; Rapp M; Azim E M; Gaudreault R C; Veyre A; Madelmont J C
CS INSERM U 71, Pavillon Saint-Francois d'Assise, Centre Hospitalier
Universitaire de Quebec.
SO DRUG METABOLISM AND DISPOSITION, (1998 Feb) 26 (2) 146-51.
Journal code: EBR; 9421550. ISSN: 0090-9556.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199803
ED Entered STN: 19980407
Last Updated on STN: 19980407
Entered Medline: 19980320
AB 1-Aryl-3-(2-chloroethyl)ureas are new agents that have shown promising
cytotoxic and antineoplastic activities. In this work, we studied the
disposition and metabolism of one of these molecules, 4-tert-butyl-[3-(2-
chloroethyl)ureido]benzene (tBCEU). tBCEU was labeled with ¹⁴C and ¹³C in
the urea function and in the chloroethyl moiety. After ip administration
of the molecule labeled in the urea function, radioactivity was widely
distributed in the whole organism, including the brain. HPLC analysis of
plasma showed that tBCEU was extensively metabolized, with <20% being
found in the plasma as unchanged tBCEU 1 hr after administration. One main
metabolite was identified by NMR and MS analysis as N-[4-(2-hydroxy-1,
1-dimethylethyl)phenyl]urea, widely conjugated to glucuronic acid. The
same metabolite was found in the urine. After administration of tBCEU
labeled in the chloroethyl moiety, the same tissue affinities were
observed, but the decrease of total radioactivity in blood and tissues was
slower than that observed for the molecule labeled in the urea function.
HPLC analysis of urine showed the presence of two main metabolites,
identified by MS as thiodiacetic acid and its sulfoxide. From these
results, we can deduce that the metabolic pathway of tBCEU involves
N-dealkylation of the urea portion of the molecule and hydroxylation of
the tert-butyl group. The strong cytochrome P450 reactivity of the carbon
adjacent to the urea portion of tBCEU is probably related to particular
sensitivity to oxidation at this position, based on the chemical structure
of tBCEU. These results can explain the fact that the cytotoxic effect of
tBCEU is not due to DNA alkylation, in contrast to that of its parent
molecule, chloroethylnitrosourea.
CT Check Tags: Animal; Male
*Antineoplastic Agents: ME, metabolism
Carbon Isotopes
Chromatography, High Pressure Liquid
Feces: CH, chemistry
*Metabolic Detoxication, Drug: PH, physiology
Mice
Mice, Inbred Strains
Molecular Structure
Phenylurea Compounds: BL, blood
*Phenylurea Compounds: ME, metabolism
Phenylurea Compounds: PK, pharmacokinetics
Spectrum Analysis, Mass
Urea: AA, analogs & derivatives
Urea: AN, analysis
Urea: CH, chemistry
Urine: CH, chemistry
RN 118202-59-8 (4-tert-butyl-(3-(2-chloroethyl)ureido)benzene);

57-13-6 (Urea)
CN 0 (Antineoplastic Agents); 0 (Carbon Isotopes); 0 (Phenylurea Compounds)

=> d his

(FILE 'HOME' ENTERED AT 17:16:32 ON 19 SEP 2001)

FILE 'REGISTRY' ENTERED AT 17:19:32 ON 19 SEP 2001

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L2 2 S L1
L3 28 S L2 FULL
L4 14 S L3 AND (1/O AND 1/X)
L5 12 S L4 AND 1/NR
L6 0 S L5 AND 1/N
L7 11 S L5 AND 2/N

FILE 'CAPLUS' ENTERED AT 17:22:38 ON 19 SEP 2001

L8 16 S L7
L9 10 S L8 AND (PHARMACEUTICAL OR PRODRUG OR DRUG OR MEDICAMENT OR CA

FILE 'MEDLINE' ENTERED AT 17:31:51 ON 19 SEP 2001

L10 4 S L7

=> s l4 not l9

4 L4
4 L7
53782 PHARMACEUTICAL
3396 PHARMACEUTICALS
56136 PHARMACEUTICAL
(PHARMACEUTICAL OR PHARMACEUTICALS)
3093 PRODRUG
3951 PRODRUGS
5393 PRODRUG
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2378692 DRUG
249820 DRUGS
2448184 DRUG
(DRUG OR DRUGS)
798 MEDICAMENT
2637 MEDICAMENTS
3366 MEDICAMENT
(MEDICAMENT OR MEDICAMENTS)
353754 CANCER
49182 CANCERS
370084 CANCER
(CANCER OR CANCERS)
10596 TUBULIN
639 TUBULINS
10684 TUBULIN
(TUBULIN OR TUBULINS)

L11 0 L4 NOT L9

=> file beilstein

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CA SUBSCRIBER PRICE	0.00	-5.88

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FILE LAST UPDATED: 6 MAR 2000

FILE COVERS 1779 TO 2000.

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*** FILE CONTAINS 7,688,486 SUBSTANCES ***

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* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS. *
* FOR PRICE INFORMATION SEE HELP COST *

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.00	212.17
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-5.88

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Sep 14, 2001 (20010914/UP).

=> file beilstein

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
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CA SUBSCRIBER PRICE	0.00	-5.88

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FILE LAST UPDATED: 6 MAR 2000

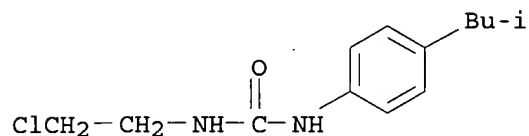
FILE COVERS 1779 TO 2000.

*** CAS REGISTRY NUMBERS FOR 4,356,237 SUBSTANCES AVAILABLE ***

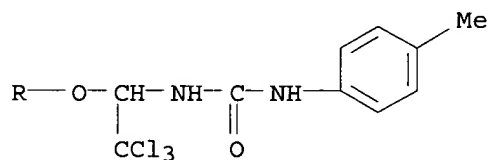
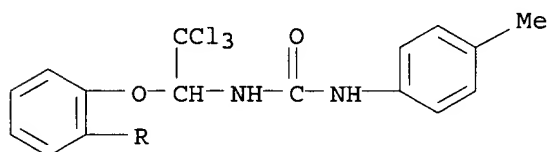
*** FILE CONTAINS 7,688,486 SUBSTANCES ***

* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST. *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS. *
* FOR PRICE INFORMATION SEE HELP COST *

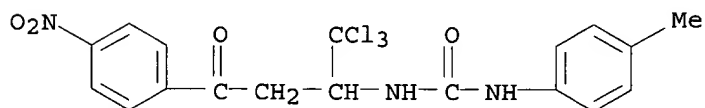
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 IN Urea, N-(2-chloroethyl)-N'-[4-(2-methylpropyl)phenyl]- (9CI)
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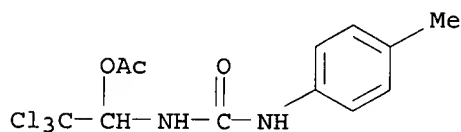
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N,N''-[1,2-phenylenebis[oxy(2,2,2-trichloroethylidene)]]bis[N'-(4-methylphenyl)]- (9CI)
 MF C26 H24 Cl6 N4 O4

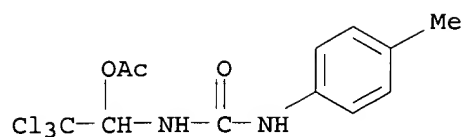


L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
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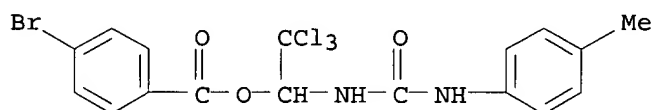


L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-[1-(acetyloxy)-2,2,2-trichloroethyl]-N'-(4-methylphenyl)- (9CI)
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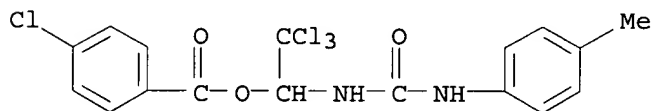




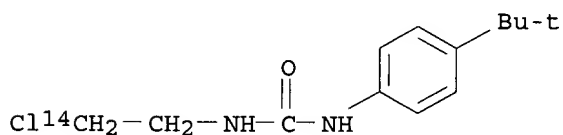
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Benzoic acid, 4-bromo-, 2,2,2-trichloro-1-[[[4-methylphenyl]amino]carbonyl]amino]ethyl ester (9CI)
 MF C17 H14 Br Cl3 N2 O3



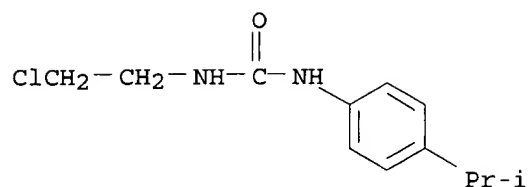
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Benzoic acid, 4-chloro-, 2,2,2-trichloro-1-[[[4-methylphenyl]amino]carbonyl]amino]ethyl ester (9CI)
 MF C17 H14 Cl4 N2 O3



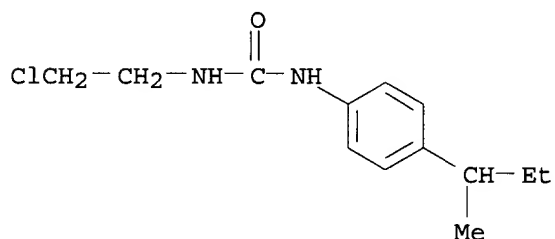
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
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 MF C13 H19 Cl N2 O



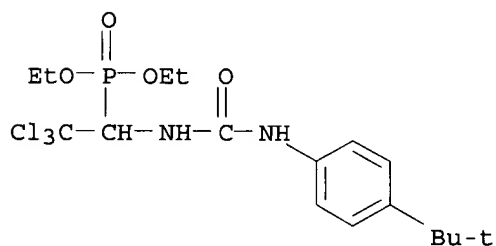
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl] - (9CI)
 MF C12 H17 Cl N2 O



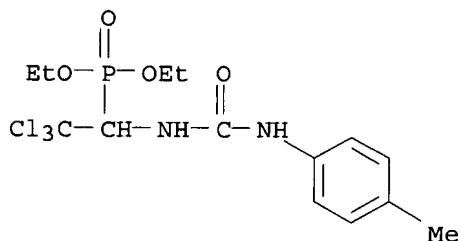
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 IN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI)
 MF C13 H19 Cl N2 O



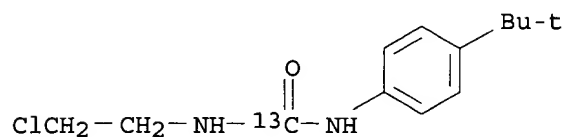
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Phosphonic acid, [2,2,2-trichloro-1-[[[4-(1,1-dimethylethyl)phenyl]amino]carbonyl]amino]ethyl]-, diethyl ester (9CI)
 MF C17 H26 Cl3 N2 O4 P



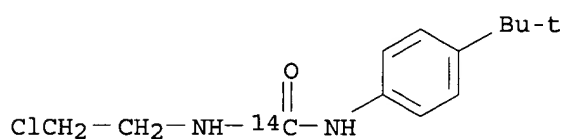
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Phosphonic acid, [2,2,2-trichloro-1-[[[4-methylphenyl]amino]carbonyl]amino]ethyl]-, diethyl ester (9CI)
 MF C14 H20 Cl3 N2 O4 P



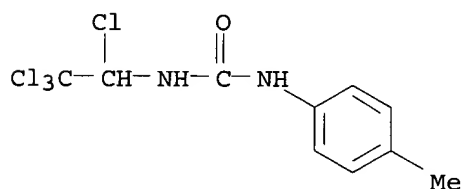
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea-13C, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl] - (9CI)
 MF C13 H19 Cl N2 O



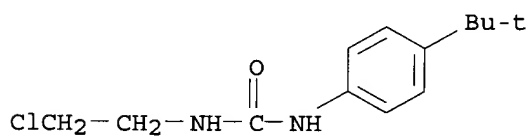
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea-14C, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl] - (9CI)
 MF C13 H19 Cl N2 O



L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(4-methylphenyl)-N'-(1,2,2,2-tetrachloroethyl) - (9CI)
 MF C10 H10 Cl4 N2 O

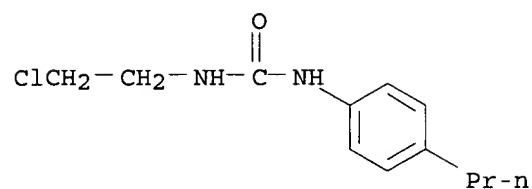


L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl] - (9CI)
 MF C13 H19 Cl N2 O

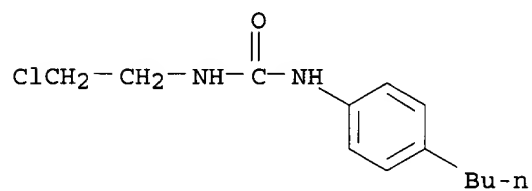


L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
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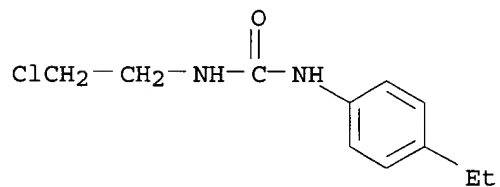
MF C12 H17 Cl N2 O



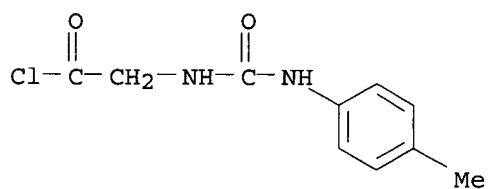
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
IN Urea, N-(4-butylphenyl)-N'-(2-chloroethyl)- (9CI)
MF C13 H19 Cl N2 O



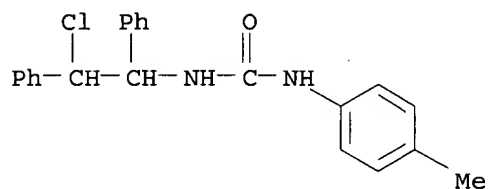
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
IN Urea, N-(2-chloroethyl)-N'-(4-ethylphenyl)- (9CI)
MF C11 H15 Cl N2 O



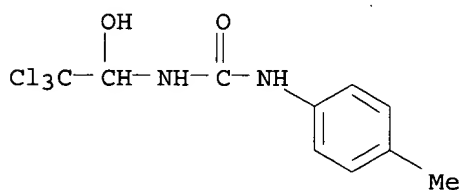
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
IN Acetyl chloride, [[[4-methylphenyl]amino]carbonyl]amino]- (9CI)
MF C10 H11 Cl N2 O2



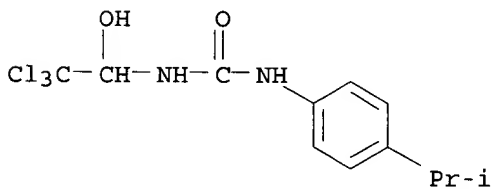
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloro-1,2-diphenylethyl)-N'-(4-methylphenyl)- (9CI)
 MF C22 H21 Cl N2 O



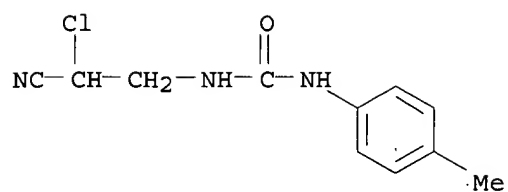
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(4-methylphenyl)-N'-(2,2,2-trichloro-1-hydroxyethyl)- (9CI)
 MF C10 H11 Cl3 N2 O2



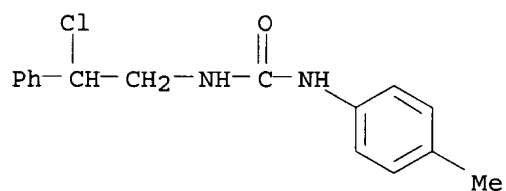
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-[4-(1-methylethyl)phenyl]-N'-(2,2,2-trichloro-1-hydroxyethyl)- (9CI)
 MF C12 H15 Cl3 N2 O2



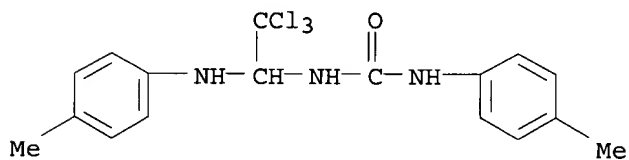
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloro-2-cyanoethyl)-N'-(4-methylphenyl)- (9CI)
 MF C11 H12 Cl N3 O



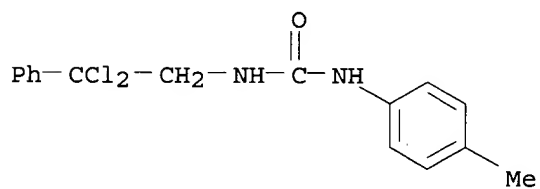
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloro-2-phenylethyl)-N'-(4-methylphenyl)- (9CI)
 MF C16 H17 Cl N2 O



L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(4-methylphenyl)-N'-[2,2,2-trichloro-1-[(4-methylphenyl)amino]ethyl]- (9CI)
 MF C17 H18 Cl3 N3 O



L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2,2-dichloro-2-phenylethyl)-N'-(4-methylphenyl)- (9CI)
 MF C16 H16 Cl2 N2 O

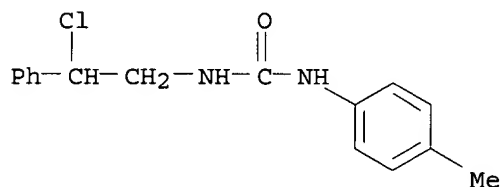


ALL ANSWERS HAVE BEEN SCANNED

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 3124228 1/X
 L4 14 L3 AND (1/O AND 1/X)

=> d scan

L4 14 ANSWERS REGISTRY COPYRIGHT 2001 ACS
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 MF C16 H17 Cl N2 O

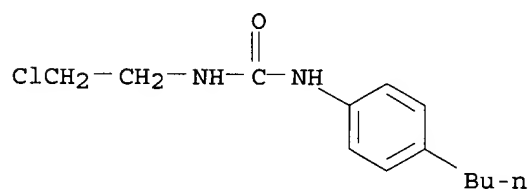


HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

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 L5 12 L4 AND 1/NR

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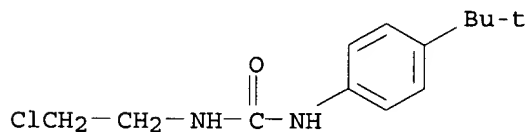
L5 12 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(4-butylphenyl)-N'-(2-chloroethyl)- (9CI)
 MF C13 H19 Cl N2 O



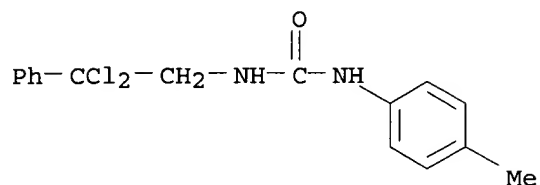
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):10

L5 12 ANSWERS REGISTRY COPYRIGHT 2001 ACS
 IN Urea, N-(2-chloroethyl)-N'-(4-propylphenyl)- (9CI)
 MF C12 H17 Cl N2 O

ACCESSION NUMBER: 1994:400339 CAPLUS
 DOCUMENT NUMBER: 121:339
 TITLE: Effect of an aryl chloroethyl urea on **tubulin** and vimentin syntheses in a human breast **cancer** cell line
 AUTHOR(S): Poyet, Patrick; Ritchot, Nathalie; Bechard, Philippe; Gaudreault, Rene C.
 CORPORATE SOURCE: Cent. Rech., Hop. Saint - Francois d'Assise, Quebec, PQ, G1L 3L5, Can.
 SOURCE: Anticancer Res. (1993), 13(5A), 1447-52
 CODEN: ANTRD4; ISSN: 0250-7005
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB A new class of antineoplastic agents, 1-aryl-3-(2-chloroethyl)ureas (CEUs), was recently developed in the authors' lab. To optimize the pharmacol. and the biol. properties of this new class of compds. and to det. its mechanism of action, at the cellular level, the authors studied the effect of 4-tert-Bu-[3-(2-chloroethyl)ureido]benzene (tBCEU) on MDA-MB-231, a human breast **cancer** hormone-independent cell line. The effect of tBCEU on protein synthesis and on the accumulation of specific mRNAs was evaluated. The results indicate that tBCEU increases the synthesis of at least two proteins present in the cytoskeleton: **tubulin** and vimentin. The effect of tBCEU on their transcripts indicates that tBCEU decreases the accumulation of **tubulin** and vimentin mRNA. These results suggest that the antineoplastic activity of tBCEU is in part related to an alteration in the synthesis pathway of **tubulin** and vimentin.
 IT 118202-59-8
 RL: BIOL (Biological study)
 (tubulin and vimentin formation inhibition by, in human breast **cancer** cell line, antitumor mechanism in relation to)
 RN 118202-59-8 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



L2 2 ANSWERS REGISTRY COPYRIGHT 2001 ACS
IN Urea, N-(2,2-dichloro-2-phenylethyl)-N'-(4-methylphenyl)- (9CI)
MF C16 H16 Cl2 N2 O



ALL ANSWERS HAVE BEEN SCANNED

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FULL SCREEN SEARCH COMPLETED - 1293 TO ITERATE

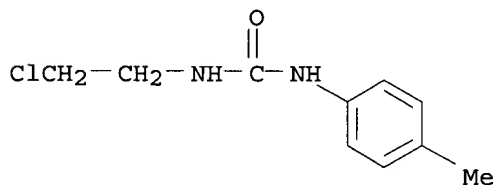
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SEARCH TIME: 00.00.04

28 ANSWERS

L3 28 SEA SSS FUL L1

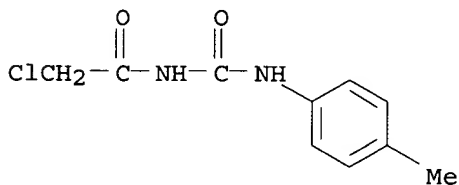
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L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
IN Urea, N-(2-chloroethyl)-N'-(4-methylphenyl)- (9CI)
MF C10 H13 Cl N2 O



HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):30

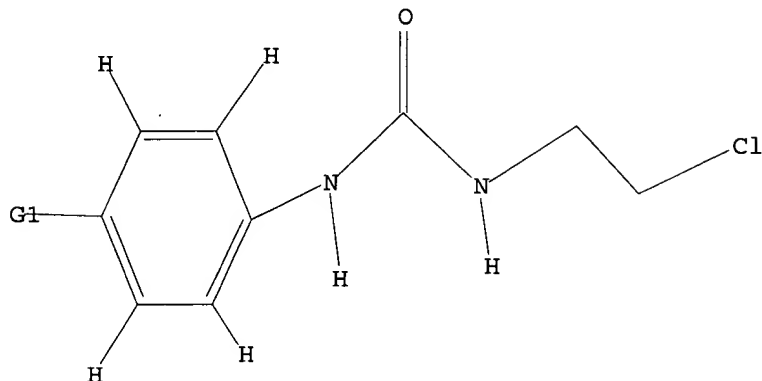
L3 28 ANSWERS REGISTRY COPYRIGHT 2001 ACS
IN Acetamide, 2-chloro-N-[[4-methylphenyl]amino]carbonyl]- (9CI)
MF C10 H11 Cl N2 O2



=>
Uploading 09741814.str

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



G1 Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, s-Bu, t-Bu

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED - 66 TO ITERATE

100.0% PROCESSED 66 ITERATIONS
SEARCH TIME: 00.00.01

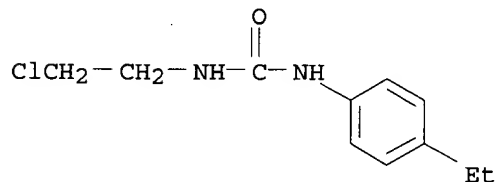
2 ANSWERS

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 833 TO 1807
PROJECTED ANSWERS: 2 TO 124

L2 2 SEA SSS SAM L1

=> d scan

L2 2 ANSWERS REGISTRY COPYRIGHT 2001 ACS
IN Urea, N-(2-chloroethyl)-N'-(4-ethylphenyl)- (9CI)
MF C11 H15 Cl N2 O



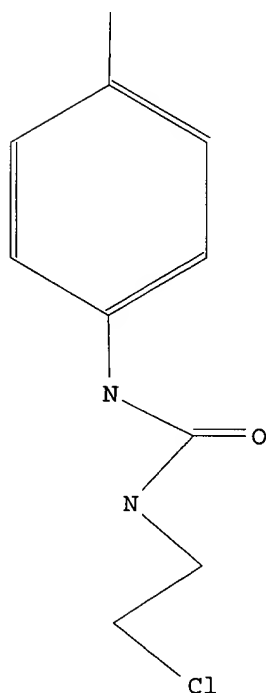
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L12 1 L7

=> d ide

L12 ANSWER 1 OF 1 COPYRIGHT 2001 BEILSTEIN CDS MDLI

Beilstein Reg. No. (BRN): 2693109 Beilstein
Molecular Formula (MF): C10 H13 Cl N2 O
Chemical Name (CN): N-<2-chloro-ethyl>-N'-p-tolyl-urea
N-<2-Chlor-aethyl>-N'-p-tolyl-harnstoff
Autonom Name (AUN): 1-(2-chloro-ethyl)-3-p-tolyl-urea
Beilstein Reference (SO): 4-12-00-01924; 5-12; 6-12
CAS Reg. No. (RN): 15145-35-4
Beilstein Pref. RN (BPR): 15145-35-4
Other Source (OS): CSEARCH
Formula Weight (FW): 212.68
Lawson Number (LN): 14141; 2826; 1762



=> d pre

L12 ANSWER 1 OF 1 COPYRIGHT 2001 BEILSTEIN CDS MDLI

Preparation:

PRE

Start: BRN=1071429 2-chloro-ethyl isocyanate, BRN=471281 p-toluidine
Reference(s):

1. Najer; Giudicelli, Bull.Soc.Chim.Fr., 1960 1650, CODEN: BSCFAS
2. Giudicelli et al., C.R.Hebd.Seances Acad.Sci., 247<1958>2494,2495, CODEN: COREAF

Note(s):

3. Handbook Data

PRE

Start: BRN=773647 2-chloro-ethylamine, BRN=471494 p-tolyl isocyanate
Reference(s):

1. Picard; McKay, Can.J.Chem., 31<1953>896,907, CODEN: CJCHAG

Note(s):

2. Handbook Data

PRE

Reference(s):

1. Najer; Giudicelli, Bull.Soc.Chim.Fr., <1960>, 1650,1651, CODEN: BSCFAS

PRE

Start: BRN=471281 4-methyl-aniline, BRN=1071429 1-chloro-2-isocyanato-ethane

Yield: 70.00 %

Solv: 1,2-dimethoxy-ethane

Reference(s):

1. Gaudreault, R. C.; Lacroix, J.; Page, M.; Joly, L. P., J.Pharm.Sci., 77
<1988> 2, 185-187, LA: EN, CODEN: JPMSAE

PRE

Start: BRN=1071429 1-chloro-2-isocyanato-ethane, BRN=471281
4-methyl-aniline

Time: 6 hour(s)

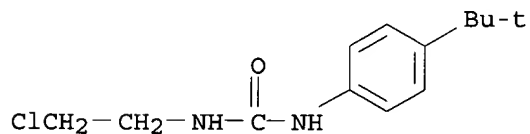
Ambient Temperature

Reference(s):

1. Bechard, P.; Lacroix, J.; Poyet, P.; C-Gaudreault, R.,
Eur.J.Med.Chem.Chim.Ther., 29 <1994> 12, 963-966, LA: EN, CODEN: EJMCA5

=>

ACCESSION NUMBER: 1994:400339 CAPLUS
 DOCUMENT NUMBER: 121:339
 TITLE: Effect of an aryl chloroethyl urea on **tubulin** and vimentin syntheses in a human breast **cancer** cell line
 AUTHOR(S): Poyet, Patrick; Ritchot, Nathalie; Bechard, Philippe; Gaudreault, Rene C.
 CORPORATE SOURCE: Cent. Rech., Hop. Saint - Francois d'Assise, Quebec, PQ, G1L 3L5, Can.
 SOURCE: Anticancer Res. (1993), 13(5A), 1447-52
 CODEN: ANTRD4; ISSN: 0250-7005
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB A new class of antineoplastic agents, 1-aryl-3-(2-chloroethyl)ureas (CEUs), was recently developed in the authors' lab. To optimize the pharmacol. and the biol. properties of this new class of compds. and to det. its mechanism of action, at the cellular level, the authors studied the effect of 4-tert-Bu-[3-(2-chloroethyl)ureido]benzene (tBCEU) on MDA-MB-231, a human breast **cancer** hormone-independent cell line. The effect of tBCEU on protein synthesis and on the accumulation of specific mRNAs was evaluated. The results indicate that tBCEU increases the synthesis of at least two proteins present in the cytoskeleton: **tubulin** and vimentin. The effect of tBCEU on their transcripts indicates that tBCEU decreases the accumulation of **tubulin** and vimentin mRNA. These results suggest that the antineoplastic activity of tBCEU is in part related to an alteration in the synthesis pathway of **tubulin** and vimentin.
 IT 118202-59-8
 RL: BIOL (Biological study)
 (tubulin and vimentin formation inhibition by, in human breast **cancer** cell line, antitumor mechanism in relation to)
 RN 118202-59-8 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



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COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	133.87	134.02

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FILE COVERS 1907 - 26 Dec 2001 VOL 135 ISS 26
 FILE LAST UPDATED: 24 Dec 2001 (20011224/ED)

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L4          17 L3

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          281393 TARGET?
L5          0 L4 AND TARGET?

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          412622 RECEPTORS
          543158 RECEPTOR
              (RECEPTOR OR RECEPTORS)
L6          1 L4 AND RECEPTOR

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L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS
 ACCESSION NUMBER: 2001:489217 CAPLUS
 DOCUMENT NUMBER: 135:71264

TITLE: Carbamidobenzenes for use as antitumor .beta.-tubulin inhibitors
 INVENTOR(S): Gaudreault, Rene C.; Legault, Jean
 PATENT ASSIGNEE(S): Universite Laval, Can.
 SOURCE: PCT Int. Appl., 43 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047504	A2	20010705	WO 2000-CA1579	20001222

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-171615 P 19991223

AB Disclosed herein are benzene carbamide .beta.-tubulin inhibitors, prodrugs thereof, and therapeutically acceptable salts thereof for use as anti-cancer cell proliferation agents.

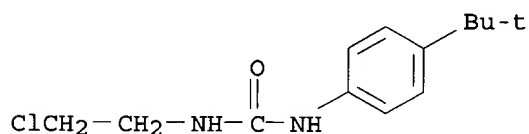
IT 118202-59-8 161194-45-2 161194-47-4

RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(carbamidobenzenes for use as antitumor .beta.-tubulin inhibitors)

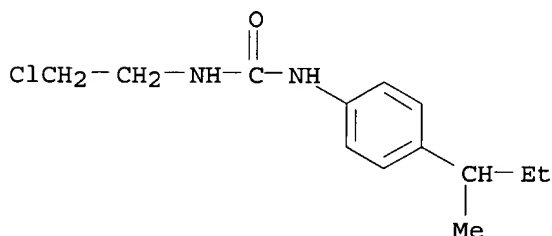
RN 118202-59-8 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



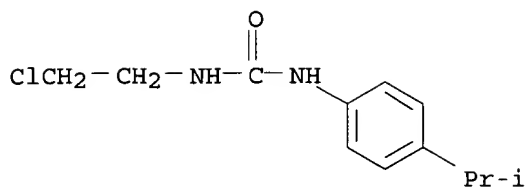
RN 161194-45-2 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



=> FIL STNGUIDE
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
8.27	142.29

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
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LAST RELOADED: Dec 14, 2001 (20011214/UP).

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FILE 'REGISTRY' ENTERED AT 07:06:15 ON 26 DEC 2001

L1 STRUCTURE UPLOADED
L2 1 S L1
L3 13 S L1 FULL

FILE 'CAPLUS' ENTERED AT 07:07:26 ON 26 DEC 2001

L4 17 S L3
L5 0 S L4 AND TARGET?
L6 1 S L4 AND RECEPTOR

FILE 'STNGUIDE' ENTERED AT 07:09:15 ON 26 DEC 2001

=> s l4 and tub?

COMBINATION OF STRUCTURE AND TEXT TERMS NOT VALID

The query entered contains both search terms created by
structure-building or screen commands and text search terms. L#s
created via the STRUCTURE or SCREEN commands must be searched in the
structures files separately from text terms or profiles. The L#
answer sets from structure searches can be used in crossover searches
and can be combined with text terms.

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.00	142.29

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
0.00	-0.59

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FILE COVERS 1907 - 26 Dec 2001 VOL 135 ISS 26
FILE LAST UPDATED: 24 Dec 2001 (20011224/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REGISTRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

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=> s l4 and tub?
499640 TUB?

L7 4 L4 AND TUB?

=> d ibib abs hitstr 1-4

L7 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:489217 CAPLUS
DOCUMENT NUMBER: 135:71264
TITLE: Carbamidobenzenes for use as antitumor .beta.-
tubulin inhibitors
INVENTOR(S): Gaudreault, Rene C.; Legault, Jean
PATENT ASSIGNEE(S): Universite Laval, Can.
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047504	A2	20010705	WO 2000-CA1579	20001222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,				

HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
 LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
 SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
 YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
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PRIORITY APPLN. INFO.: US 1999-171615 P 19991223

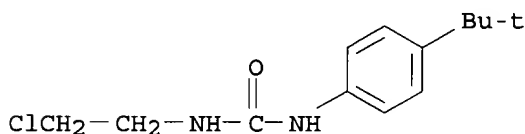
AB Disclosed herein are benzene carbamide .beta.-**tubulin**
 inhibitors, prodrugs thereof, and therapeutically acceptable salts thereof
 for use as anti-cancer cell proliferation agents.

IT 118202-59-8 161194-45-2 161194-47-4

RL: BAC (Biological activity or effector, except adverse); PEP (Physical,
 engineering or chemical process); THU (Therapeutic use); BIOL (Biological
 study); PROC (Process); USES (Uses)
 (carbamidobenzenes for use as antitumor .beta.-**tubulin**
 inhibitors)

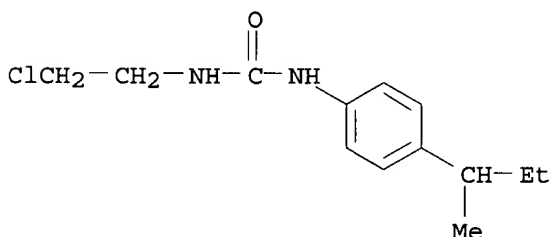
RN 118202-59-8 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX
 NAME)



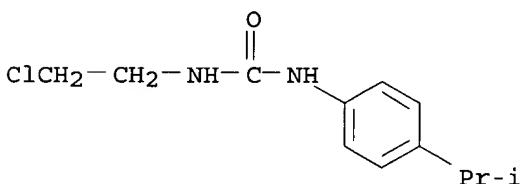
RN 161194-45-2 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX
 NAME)



RN 161194-47-4 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX
 NAME)



L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:55542 CAPLUS

DOCUMENT NUMBER: 134:246870

TITLE: Antimitotic antitumor agents: synthesis,

structure-activity relationships, and biological characterization of N-aryl-N'-(2-chloroethyl)ureas as new selective alkylating agents

AUTHOR(S): Mounetou, Emmanuelle; Legault, Jean; Lacroix, Jacques; C-Gaudreault, Rene

CORPORATE SOURCE: Centre de Recherche, CHUQ Hopital Saint-Francois d'Assise, QC, G1L3L5, Can.

SOURCE: Journal of Medicinal Chemistry (2001), 44(5), 694-702
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A series of N-aryl-N'-(2-chloroethyl) ureas (CEUs) and derivs. were synthesized and evaluated for antiproliferative activity against a wide panel of tumor cell lines. Systematic structure-activity relationship (SAR) studies indicated that: (i) a branched alkyl chain or a halogen at the 4-position of the Ph ring or a fluorenyl/indanyl group, (ii) an exocyclic urea function, and (iii) a N'-2-chloroethyl moiety were required to ensure significant cytotoxicity. Biol. expts., such as immunofluorescence microscopy, confirmed that these promising compds. alter the cytoskeleton by inducing microtubule depolymn. via selective alkylation of .beta.-**tubulin**. Subsequent evaluations demonstrated that potent CEUs were weak alkylators, were non-DNA-damaging agents, and did not interact with the thiol function of either glutathione or glutathione reductase. Therefore, CEUs are part of a new class of antimitotic agents. Finally, among the series of CEUs evaluated, compds. N' 4-isopropylphenyl, 4-sec-butylphenyl, 4-tert-butylphenyl, and 4-iodophenyl N-(2-chloroethyl)ureas were selected for further in vivo trials.

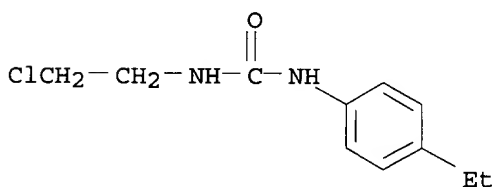
IT 102433-48-7 113849-19-7 118202-58-7
118202-59-8 161194-45-2 161194-47-4
331171-31-4

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(synthesis, SAR, and biol. characterization of arylchloroethyl ureas as new selective alkylating agents)

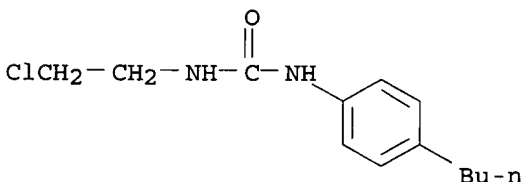
RN 102433-48-7 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-(4-ethylphenyl)- (9CI) (CA INDEX NAME)



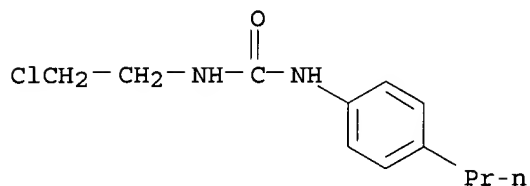
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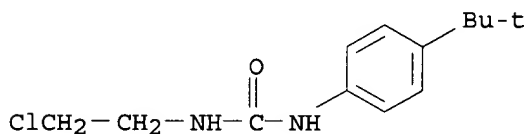
RN 118202-58-7 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-(4-propylphenyl)- (9CI) (CA INDEX NAME)



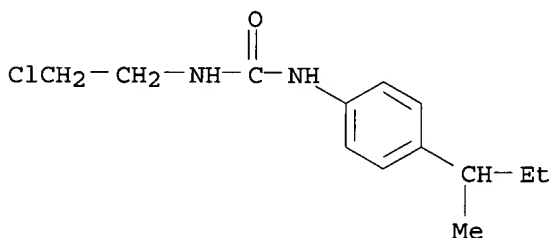
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CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



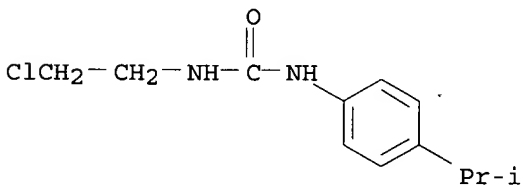
RN 161194-45-2 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



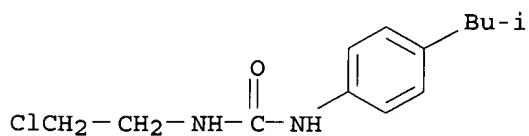
RN 161194-47-4 CAPLUS

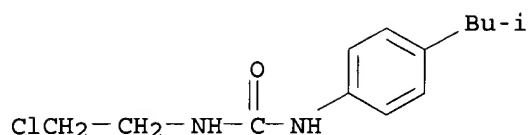
CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 331171-31-4 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(2-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)





REFERENCE COUNT: 22
 REFERENCE(S): (1) Bardos, T; J Med Chem 1965, V8, P167 CAPLUS
 (2) Becker, K; Methods Enzymol 1995, V251, P173 CAPLUS
 (4) Cohen, M; Biochem Pharmacol 1988, V37, P3317 CAPLUS
 (5) Ellman, G; Arch Biochem Biophys 1959, V82, P70 CAPLUS
 (6) Frischer, H; J Clin Invest 1993, V92, P2761 CAPLUS
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:160216 CAPLUS

DOCUMENT NUMBER: 132:302978

TITLE: Microtubule disruption induced in vivo by alkylation of .beta.-**tubulin** by 1-aryl-3-(2-chloroethyl)ureas, a novel class of soft alkylating agents

AUTHOR(S): Legault, Jean; Gaulin, Jean-Francois; Mounetou, Emmanuelle; Bolduc, Sebastien; Lacroix, Jacques; Poyet, Patrick; Gaudreault, Rene C.

CORPORATE SOURCE: Biotechnology Unit, Biomaterial Institute of Quebec, Centre Hospitalier Universitaire de Quebec, Laval University, Quebec City, PQ, G1L 3L5, Can.

SOURCE: Cancer Res. (2000), 60(4), 985-992

CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: AACR Subscription Office

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have previously reported that 4-tert-butyl-[3-(2-chloroethyl)ureido] benzene (4-tBCEU), a potent cytotoxic agent, modulates the synthesis of **tubulins**, suggesting that its cytotoxicity may be mediated through an antimicrotubule mechanism. Indeed, 4-t-BCEU and its 4-iso-Pr (4-iso-Pr [3-(2-chloroethyl)ureido] benzene) and 4-sec-Bu (4-sec-Bu [3-(2-chloroethyl)ureido] benzene) homologues induced disruption of the cytoskeleton and arrest of the cell cycle in G2 transition and mitosis. To better understand the mechanisms responsible for microtubule disruption by 1-aryl-3-(2-chloroethyl)ureas (CEU), we first examd. their cytotoxicity on Chinese hamster ovary cells resistant to vinblastine and colchicine due to the expression of mutated **tubulins** (CHO-VV 3-2). These cells showed resistance to CEU, e.g., 4-tBCEU having an IC50 of 21.3 +/- 1.1 .mu.M as compared with an IC50 of 11.6 +/- 0.7 .mu.M for wild-type cells, suggesting a direct effect of the drugs on **tubulins**. Western blot anal. confirmed the disruption of microtubules and evidenced the formation of an addnl. immunoreactive .beta.-**tubulin** with an apparent lower mol. wt. on SDS polyacrylamide gel. Incubation of MDA-MB-231 cells with [urea-14C]-4-tBCEU revealed the presence of a radioactive protein that coincided with the addnl. .beta.-**tubulin** band, indicating that CEU could covalently bind to the .beta.-**tubulin**. The 4-tBCEU-binding site on .beta.-**tubulin** was identified by competition of the CEU with colchicine, vinblastine, and iodoacetamide, a specific alkylating agent of sulfhydryl groups of cysteine residues. Colchicine, but not vinblastine, prevented the formation of the addnl. .beta.-**tubulin** band, suggesting that 4-tBCEU alkylates either Cys239 or Cys354 residues near the colchicine-binding site. To det. the cysteine residue alkylated by 4-tBCEU, we incubated the radiolabeled drug with human neuroblastoma cells (SK-N-SH) that overexpress the .beta.III-**tubulin**, an isoform

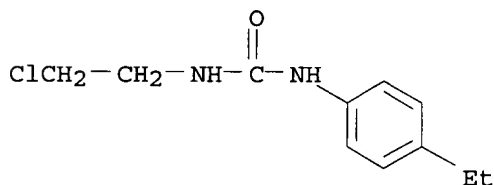
where Cys239 is replaced by a serine residue. The results clearly showed that .beta.III-**tubulin** is not alkylated by [urea-14C]-4-tBCEU, suggesting that cysteine 239 residue is essential for the reactivity of 4-tBCEU with .beta.-**tubulin**. Taken together, these findings indicate that the mechanism of cytotoxicity of CEU involves microtubule depolymn. through alkylation of .beta.-**tubulin**.

IT 102433-48-7 113849-19-7 118202-59-8
161194-45-2 161194-47-4

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(microtubule disruption induced by .beta.-**tubulin** alkylation by 1-aryl-3-(2-chloroethyl)ureas, novel class of soft alkylating agents)

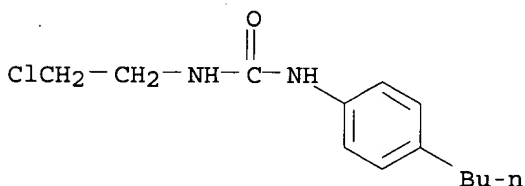
RN 102433-48-7 CAPLUS

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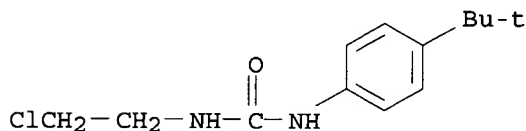
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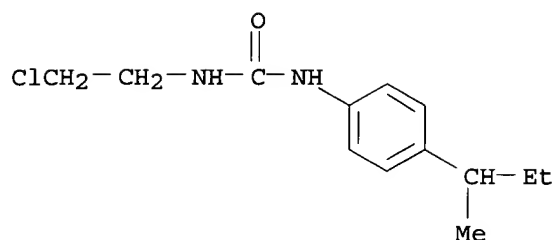
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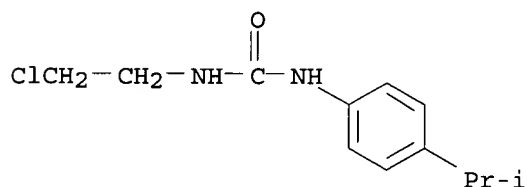


RN 161194-45-2 CAPLUS

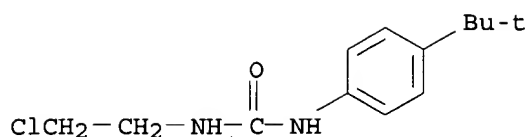
CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



L7 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2001 ACS
 ACCESSION NUMBER: 1994:400339 CAPLUS
 DOCUMENT NUMBER: 121:339
 TITLE: Effect of an aryl chloroethyl urea on **tubulin** and vimentin syntheses in a human breast cancer cell line
 AUTHOR(S): Poyet, Patrick; Ritchot, Nathalie; Bechard, Philippe; Gaudreault, Rene C.
 CORPORATE SOURCE: Cent. Rech., Hop. Saint - Francois d'Assise, Quebec, PQ, G1L 3L5, Can.
 SOURCE: Anticancer Res. (1993), 13(5A), 1447-52
 CODEN: ANTRD4; ISSN: 0250-7005
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB A new class of antineoplastic agents, 1-aryl-3-(2-chloroethyl)ureas (CEUs), was recently developed in the authors' lab. To optimize the pharmacol. and the biol. properties of this new class of compds. and to det. its mechanism of action, at the cellular level, the authors studied the effect of 4-tert-Bu-[3-(2-chloroethyl)ureido]benzene (tBCEU) on MDA-MB-231, a human breast cancer hormone-independent cell line. The effect of tBCEU on protein synthesis and on the accumulation of specific mRNAs was evaluated. The results indicate that tBCEU increases the synthesis of at least two proteins present in the cytoskeleton: **tubulin** and vimentin. The effect of tBCEU on their transcripts indicates that tBCEU decreases the accumulation of **tubulin** and vimentin mRNA. These results suggest that the antineoplastic activity of tBCEU is in part related to an alteration in the synthesis pathway of **tubulin** and vimentin.
 IT 118202-59-8
 RL: BIOL (Biological study)
 (tubulin and vimentin formation inhibition by, in human breast cancer cell line, antitumor mechanism in relation to)
 RN 118202-59-8 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



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L4 17 S L3
L5 0 S L4 AND TARGET?
L6 1 S L4 AND RECEPTOR

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FILE 'CAPLUS' ENTERED AT 07:12:01 ON 26 DEC 2001

L7 4 S L4 AND TUB?

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L4 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2001 ACS

TI Membrane interactions of a new class of anticancer agents derived from arylchloroethylurea: a FTIR spectroscopic study

L4 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2001 ACS

TI Carbamidobenzenes for use as antitumor .beta.-tubulin inhibitors

L4 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2001 ACS

TI Antimitotic antitumor agents: synthesis, structure-activity relationships, and biological characterization of N-aryl-N'-(2-chloroethyl)ureas as new selective alkylating agents

L4 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2001 ACS

TI Microtubule disruption induced in vivo by alkylation of .beta.-tubulin by 1-aryl-3-(2-chloroethyl)ureas, a novel class of soft alkylating agents

L4 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2001 ACS

TI Interaction between lipid bilayers and a new class of antineoplastic agents derived from arylchloroethylurea: a 2H solid-state NMR study

L4 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2001 ACS

TI Disposition and metabolism of a novel antineoplastic agent, 4-tert-butyl-[3-(2-chloroethyl)ureido]benzene, in mice

L4 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2001 ACS

TI Synthesis of 4-tert-butyl-3-(2-chloro-[2-¹⁴C]ethyl)ureido benzene

L4 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2001 ACS

TI Interaction of antineoplastic drug 4-tert-butyl-[3-(2-chloroethyl) ureido] benzene with phosphatidylcholine bilayers: a differential scanning calorimetry and infrared spectroscopy study

L4 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2001 ACS

TI Preparation of arylurea derivatives and analogs as anticancer agents

L4 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2001 ACS
 TI Synthesis and cytotoxic activity of new alkyl[3-(2-chloroethyl)ureido]benzene derivatives

L4 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2001 ACS
 TI Lack of cross-resistance to a new cytotoxic arylchloroethyl urea in various drug-resistant tumor cells

L4 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2001 ACS
 TI Effect of an aryl chloroethyl urea on tubulin and vimentin syntheses in a human breast cancer cell line

L4 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2001 ACS
 TI .alpha.-Substituted phosphonates. 68. .alpha.-Aminophosphonates and phosphono-substituted heterocycles from diethyl (2,2,2-trichloro-1-isocyanatoethyl)phosphonate

L4 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2001 ACS
 TI Labeling 4-tert-butylphenyl(chloroethyl)urea with carbon-14 and carbon-13

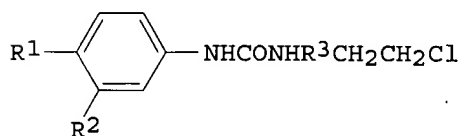
L4 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2001 ACS
 TI In vitro and in vivo activity of 1-aryl-3-(2-chloroethyl)urea derivatives as new antineoplastic agents

L4 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2001 ACS
 TI 1-Aryl-3-(2-chloroethyl)ureas: synthesis and in vitro assay as potential anticancer agents

L4 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2001 ACS
 TI Pressure- or heat-sensitive recording material

=> d ibib abs hitstr 14 16 14 12 11 9 6 1 2 4

L4 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2001 ACS
 ACCESSION NUMBER: 1988:161014 CAPLUS
 DOCUMENT NUMBER: 108:161014
 TITLE: 1-Aryl-3-(2-chloroethyl)ureas: synthesis and in vitro assay as potential anticancer agents
 AUTHOR(S): Gaudreault, R. C.; Lacroix, J.; Page, M.; Joly, L. P.
 CORPORATE SOURCE: Fac. Med., Univ. Laval, Ste-Foy, PQ, G1K 7P4, Can.
 SOURCE: J. Pharm. Sci. (1988), 77(2), 185-7
 CODEN: JPMSAE; ISSN: 0022-3549
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 108:161014
 GI



AB 1-Aryl-3-(2-chloroethyl)ureas [I, R1 = (CH2)3CO2Me, (CH2)3CO2H, Bu or Me, R2 = H, or NHCONH(CH2)2Cl, R3 = H] and 1-aryl-3-nitroso-3-(2-chloroethyl)ureas [I, R1 = Me, or (CH2)3CO2Me, R2 = H or NHCONH(NO)(CH2)2Cl, R3 = NO], were synthesized starting from 4-phenylbutyric acid, via nitration, esterification, redn., 2-chloroethyl isocyanate treatment and nitrosation, and their cytotoxicity was evaluated

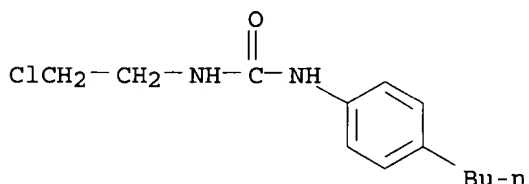
on human adenocarcinoma cells in vitro. I [R1 = (CH₂)₃CO₂Me, R2 = R3 = H], I (R1 = Me, R2 = R3 = H), and I (R1 = Bu, R2 = R3 = H) were at least as cytotoxic as chlorambucil while their N-nitroso derivs. were inactive.

IT 113849-19-7P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and antitumor activity of)

RN 113849-19-7 CAPLUS

CN Urea, N-(4-butylphenyl)-N'-(2-chloroethyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1994:216885 CAPLUS

DOCUMENT NUMBER: 120:216885

TITLE: Labeling 4-tert-butylphenyl(chloroethyl)urea with carbon-14 and carbon-13

AUTHOR(S): Azim, M.; Madelmont, J. C.; Cussac, C.; Rapp, M.; Maurizis, J. C.; Gaudreault, R. G.; Godeneche, D.; Veyre, A.

CORPORATE SOURCE: U 71, INSERM, Clermont-Ferrand, 63005, Fr.

SOURCE: J. Labelled Compd. Radiopharm. (1993), 33(11), 1079-82
CODEN: JLCRD4; ISSN: 0362-4803

DOCUMENT TYPE: Journal

LANGUAGE: French

OTHER SOURCE(S): CASREACT 120:216885

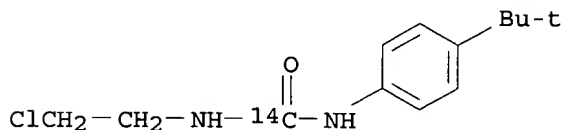
AB The labeling of 2-chloroethyl isocyanate with ¹⁴C and ¹³C on the carbonyl group from 3-chloropropionic acid ¹⁴C and ¹³C is described. This isocyanate was used to prep. 4-tert-butyl-1-[3-(2-chloroethyl)ureido]benzene.

IT 153942-01-9P 153942-02-0P

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

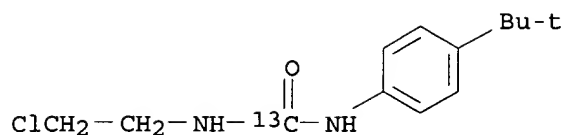
RN 153942-01-9 CAPLUS

CN Urea-¹⁴C, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 153942-02-0 CAPLUS

CN Urea-¹³C, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



L4 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1994:400339 CAPLUS

DOCUMENT NUMBER: 121:339

TITLE: Effect of an aryl chloroethyl urea on tubulin and vimentin syntheses in a human breast cancer cell line
 AUTHOR(S): Poyet, Patrick; Ritchot, Nathalie; Bechard, Philippe; Gaudreault, Rene C.

CORPORATE SOURCE: Cent. Rech., Hop. Saint - Francois d'Assise, Quebec, PQ, G1L 3L5, Can.

SOURCE: Anticancer Res. (1993), 13(5A), 1447-52

CODEN: ANTRD4; ISSN: 0250-7005

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A new class of antineoplastic agents, 1-aryl-3-(2-chloroethyl)ureas (CEUs), was recently developed in the authors' lab. To optimize the pharmacol. and the biol. properties of this new class of compds. and to det. its mechanism of action, at the cellular level, the authors studied the effect of 4-tert-Bu-[3-(2-chloroethyl)ureido]benzene (tBCEU) on MDA-MB-231, a human breast cancer hormone-independent cell line. The effect of tBCEU on protein synthesis and on the accumulation of specific mRNAs was evaluated. The results indicate that tBCEU increases the synthesis of at least two proteins present in the cytoskeleton: tubulin and vimentin. The effect of tBCEU on their transcripts indicates that tBCEU decreases the accumulation of tubulin and vimentin mRNA. These results suggest that the antineoplastic activity of tBCEU is in part related to an alteration in the synthesis pathway of tubulin and vimentin.

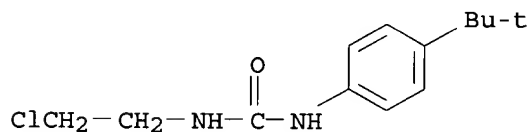
IT 118202-59-8

RL: BIOL (Biological study)

(tubulin and vimentin formation inhibition by, in human breast cancer cell line, antitumor mechanism in relation to)

RN 118202-59-8 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



L4 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1994:645277 CAPLUS

DOCUMENT NUMBER: 121:245277

TITLE: Lack of cross-resistance to a new cytotoxic arylchloroethyl urea in various drug-resistant tumor cells

AUTHOR(S): Gaudreault, Rene C.; Alaoui-Jamali, Moulay A.; Batist, Gerald; Bechard, Philippe; Lacroix, Jacques; Poyet, Patrick

CORPORATE SOURCE: Cent. de recherche, Hop. St. d'Assise, PQ, G1L 3L5, Can.

SOURCE: Cancer Chemother. Pharmacol. (1994), 33(6), 489-92

CODEN: CCPHDZ; ISSN: 0344-5704

DOCUMENT TYPE: Journal
LANGUAGE: English

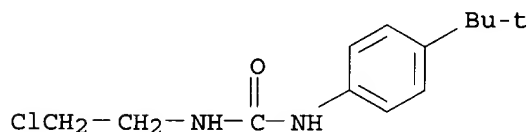
AB 1-Aryl 3-(2-chloroethyl) ureas (CEUs), a new class of potent antineoplastic agents, were recently developed in our lab. These compds. were designed from the arom. moiety of chlorambucil and the unnitrosated pharmacophore of carmustine. In the present study we investigated the effect of the potent CEU deriv. 4-tert-butyl-[3-(2-chloroethyl)ureido] benzene (tBCEU) on tumor cell lines selected for resistance to a wide range of anticancer drugs. The resistance mechanisms found in these cells included increased expression of P-glycoprotein, increased intracellular concn. of glutathione and/or glutathione-S-transferase activity, alteration of topoisomerase II, and increased DNA repair. Whereas the resistant cell lines were found to be highly resistant to a panel of clin. known anticancer drugs, tBCEU was found to be equally cytotoxic to both resistant and parental cells. The nitrobenzylpyridine assay indicated that tBCEU is a weaker alkylating agent than chlorambucil. This lack of cross-resistance in various resistant tumor cells suggests that tBCEU could be potentially useful in the treatment of cancers resistant to conventional anticancer drugs.

IT 118202-59-8

RL: BIOL (Biological study)
(antitumor effect in various drug-resistant cells, lack of cross-resistance to)

RN 118202-59-8 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



L4 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1995:380362 CAPLUS

DOCUMENT NUMBER: 122:239336

TITLE: Preparation of arylurea derivatives and analogs as anticancer agents

INVENTOR(S): C.-Gaudreault, Rene; Poyet, Patrick

PATENT ASSIGNEE(S): Universite Laval, Can.

SOURCE: Can. Pat. Appl., 25 pp.

CODEN: CPXXEB

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

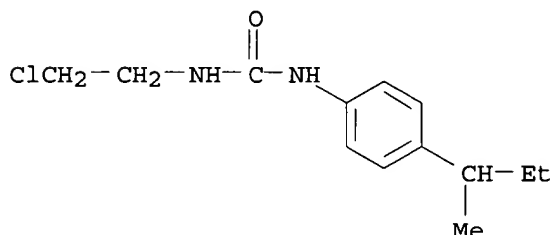
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2116621	AA	19940904	CA 1994-2116621	19940228
US 5530026	A	19960625	US 1995-369584	19950106
US 5750547	A	19980512	US 1996-664233	19960607
PRIORITY APPLN. INFO.:			US 1993-25848	19930303
			US 1995-369584	19950106

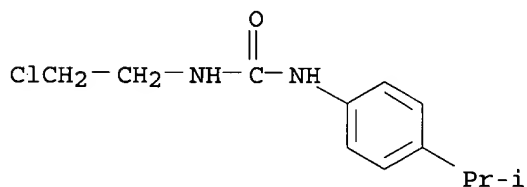
OTHER SOURCE(S): MARPAT 122:239336

AB Title compds. BACONHCH₂CH₂Cl (I; A = O, NH; B = Ph, indane, fluorene, indazole, indole, and pyridine, optionally substituted, prodrug, with provisos), are prepd,. I have antineoplastic activity without systemic toxicity and mutagenicity. To 4-sec-butylaniline in Et₂O was added 2-chloroethyl isocyanate to give I (B = 4-(EtCHMe)C₆H₄, A = NH). Anticancer activity was demonstrated.

IT 161194-45-2P 161194-47-4P
 RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of arylurea derivs. and analogs as anticancer agents)
 RN 161194-45-2 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



L4 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2001 ACS
 ACCESSION NUMBER: 1998:129113 CAPLUS
 DOCUMENT NUMBER: 128:252464
 TITLE: Disposition and metabolism of a novel antineoplastic agent, 4-tert-butyl-[3-(2-chloroethyl)ureido]benzene, in mice
 AUTHOR(S): Maurizis, Jean-Claude; Rapp, Maryse; Azim, El Mostafa; Gaudreault, Rene C.; Veyre, Annie; Madelmont, Jean-Claude
 CORPORATE SOURCE: INSERM U 71, Clermont-Ferrand, 63005, Fr.
 SOURCE: Drug Metab. Dispos. (1998), 26(2), 146-151
 CODEN: DMDSAI; ISSN: 0090-9556
 PUBLISHER: Williams & Wilkins
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB 1-Aryl-3-(2-chloroethyl)ureas are new agents that have shown promising cytotoxic and antineoplastic activities. In this work, we studied the disposition and metab. of one of these mols., 4-tert-butyl-[3-(2-chloroethyl)ureido]benzene (tBCEU). tBCEU was labeled with ¹⁴C and ¹³C in the urea function and in the chloroethyl moiety. After i.p. administration of the mol. labeled in the urea function, radioactivity was widely distributed in the whole organism, including the brain. HPLC anal. of plasma showed that tBCEU was extensively metabolized, with <20% being found in the plasma as unchanged tBCEU 1 h after administration. One main metabolite was identified by NMR and MS anal. as N-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]urea, widely conjugated to glucuronic acid. The same metabolite was found in the urine. After administration of tBCEU labeled in the chloroethyl moiety, the same tissue affinities were obsd., but the

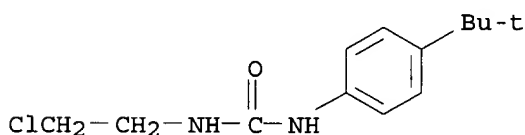
decrease of total radioactivity in blood and tissues was slower than that obsd. for the mol. labeled in the urea function. HPLC anal. of urine showed the presence of two main metabolites, identified by MS as thiodiacetic acid and its sulfoxide. From these results, we can deduce that the metabolic pathway of tBCEU involves N-dealkylation of the urea portion of the mol. and hydroxylation of the tert-Bu group. The strong cytochrome P 450 reactivity of the carbon adjacent to the urea portion of tBCEU is probably related to particular sensitivity to oxidn. at this position, based on the chem. structure of tBCEU. These results can explain the fact that the cytotoxic effect of tBCEU is not due to DNA alkylation, in contrast to that of its parent mol., chloroethylnitrosourea.

IT 118202-59-8

RL: BPR (Biological process); BIOL (Biological study); PROC (Process) (disposition and metab. of antineoplastic agent, 4-tert-butyl-[3-(2-chloroethyl)ureido]benzene, in mice)

RN 118202-59-8 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



L4 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:518931 CAPLUS

DOCUMENT NUMBER: 135:366376

TITLE: Membrane interactions of a new class of anticancer agents derived from arylchloroethylurea: a FTIR spectroscopic study

AUTHOR(S): Saint-Laurent, A.; Boudreau, N.; Lariviere, D.; Legault, J.; Gaudreault, R. C.; Auger, M.

CORPORATE SOURCE: Departement de Chimie, CERSIM, Universite Laval, Quebec, QC, G1K 7P4, Can.

SOURCE: Chem. Phys. Lipids (2001), 111(2), 163-175

CODEN: CPLIA4; ISSN: 0009-3084

PUBLISHER: Elsevier Science Ireland Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have investigated the interaction between a new class of antineoplastic agents derived from arylchloroethylurea (CEU) and different lipids such as dimyristoylphosphatidylcholine (DMPC) in the absence and presence of 30 mol% of cholesterol, dimyristoylphosphatidylglycerol (DMPG) and a mixt. made of 1-palmitoyl-2-oleoylphosphatidylcholine (POPC) and DMPC by Fourier transform IR (FTIR) spectroscopy. The results indicate that the drugs incorporate in the bilayer and cause a decrease of the phase transition temp. and an increase of the conformational disorder of the lipid acyl chains. These effects are dependent on the nature (degree of branching, length of the alkyl chain and presence of a sulfur atom), as well as on the position of the R substituent and are related to the cytotoxicity of the drugs. More specifically, the more cytotoxic drugs, such as 4-sec-Bu CEU, are those having a bulky branched substituent and those for which the disordering effect on the lipid bilayer is the greatest. On the other hand, the disordering effect is small for the long chain CEUs, such as 4-n-hexadecyl CEU, which have been shown to have weak cytotoxic activity.

IT 102433-48-7 113849-19-7 118202-59-8

161194-45-2 161194-47-4

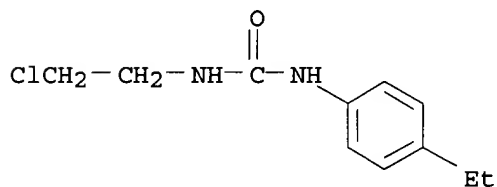
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological

study); PROC (Process); USES (Uses)

(membrane interactions of a new class of anticancer agents derived from
arylchloroethylurea)

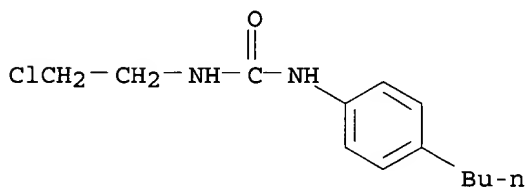
RN 102433-48-7 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-(4-ethylphenyl)- (9CI) (CA INDEX NAME)



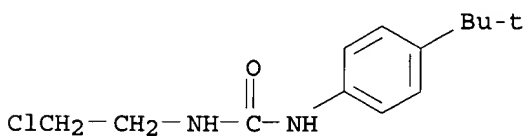
RN 113849-19-7 CAPLUS

CN Urea, N-(4-butylphenyl)-N'-(2-chloroethyl)- (9CI) (CA INDEX NAME)



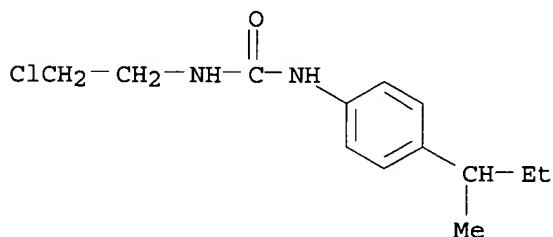
RN 118202-59-8 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



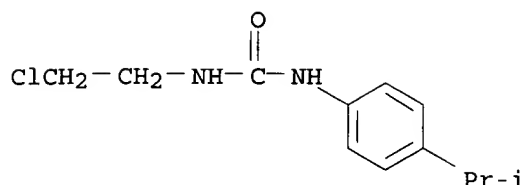
RN 161194-45-2 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)

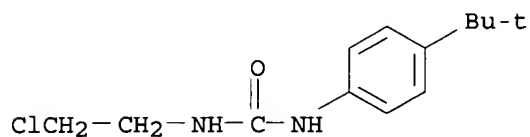


REFERENCE COUNT: 41
 REFERENCE(S): (1) Asher, I; Biochim Biophys Acta 1977, V468, P63 CAPLUS
 (5) Bouchard, M; Biochim Biophys Acta 1996, V1282, P233 CAPLUS
 (8) Cameron, D; Appl Spectrosc 1982, V36, P245 CAPLUS
 (9) Cameron, D; Biochemistry 1980, V19, P3665 CAPLUS
 (10) Casal, H; Biochim Biophys Acta 1984, V779, P381 CAPLUS
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

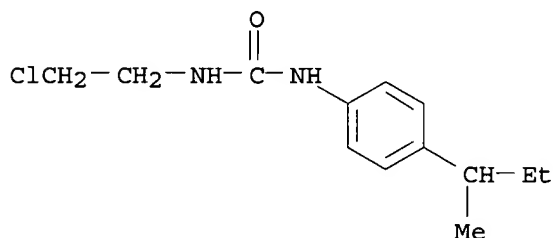
L4 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2001 ACS
 ACCESSION NUMBER: 2001:489217 CAPLUS
 DOCUMENT NUMBER: 135:71264
 TITLE: Carbamidobenzenes for use as antitumor .beta.-tubulin inhibitors
 INVENTOR(S): Gaudreault, Rene C.; Legault, Jean
 PATENT ASSIGNEE(S): Universite Laval, Can.
 SOURCE: PCT Int. Appl., 43 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047504	A2	20010705	WO 2000-CA1579	20001222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

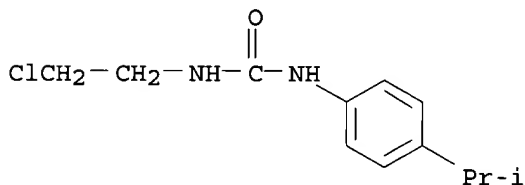
PRIORITY APPLN. INFO.: US 1999-171615 P 19991223
 AB Disclosed herein are benzene carbamide .beta.-tubulin inhibitors, prodrugs thereof, and therapeutically acceptable salts thereof for use as anti-cancer cell proliferation agents.
 IT 118202-59-8 161194-45-2 161194-47-4
 RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
 (carbamidobenzenes for use as antitumor .beta.-tubulin inhibitors)
 RN 118202-59-8 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-45-2 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CAPLUS
 CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



L4 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2001 ACS
 ACCESSION NUMBER: 2000:160216 CAPLUS
 DOCUMENT NUMBER: 132:302978
 TITLE: Microtubule disruption induced in vivo by alkylation of .beta.-tubulin by 1-aryl-3-(2-chloroethyl)ureas, a novel class of soft alkylating agents
 AUTHOR(S): Legault, Jean; Gaulin, Jean-Francois; Mounetou, Emmanuelle; Bolduc, Sebastien; Lacroix, Jacques; Poyet, Patrick; Gaudreault, Rene C.
 CORPORATE SOURCE: Biotechnology Unit, Biomaterial Institute of Quebec, Centre Hospitalier Universitaire de Quebec, Laval University, Quebec City, PQ, G1L 3L5, Can.
 SOURCE: Cancer Res. (2000), 60(4), 985-992
 CODEN: CNREA8; ISSN: 0008-5472
 PUBLISHER: AACR Subscription Office
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB We have previously reported that 4-tert-butyl-[3-(2-chloroethyl)ureido] benzene (4-tBCEU), a potent cytotoxic agent, modulates the synthesis of tubulins, suggesting that its cytotoxicity may be mediated through an antimicrotubule mechanism. Indeed, 4-t-BCEU and its 4-iso-Pr (4-iso-Pr [3-(2-chloroethyl)ureido] benzene) and 4-sec-Bu (4-sec-Bu [3-(2-chloroethyl)ureido] benzene) homologues induced disruption of the cytoskeleton and arrest of the cell cycle in G2 transition and mitosis. To better understand the mechanisms responsible for microtubule disruption by 1-aryl-3-(2-chloroethyl)ureas (CEU), we first examd. their cytotoxicity

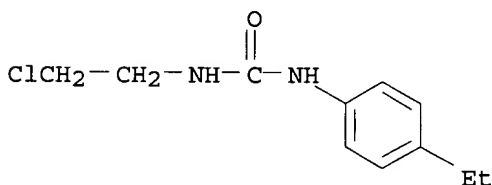
on Chinese hamster ovary cells resistant to vinblastine and colchicine due to the expression of mutated tubulins (CHO-VV 3-2). These cells showed resistance to CEU, e.g., 4-tBCEU having an IC50 of 21.3 \pm 1.1 μ M as compared with an IC50 of 11.6 \pm 0.7 μ M for wild-type cells, suggesting a direct effect of the drugs on tubulins. Western blot anal. confirmed the disruption of microtubules and evidenced the formation of an addnl. immunoreactive β -tubulin with an apparent lower mol. wt. on SDS polyacrylamide gel. Incubation of MDA-MB-231 cells with [urea-14C]-4-tBCEU revealed the presence of a radioactive protein that coincided with the addnl. β -tubulin band, indicating that CEU could covalently bind to the β -tubulin. The 4-tBCEU-binding site on β -tubulin was identified by competition of the CEU with colchicine, vinblastine, and iodoacetamide, a specific alkylating agent of sulphydryl groups of cysteine residues. Colchicine, but not vinblastine, prevented the formation of the addnl. β -tubulin band, suggesting that 4-tBCEU alkylates either Cys239 or Cys354 residues near the colchicine-binding site. To det. the cysteine residue alkylated by 4-tBCEU, we incubated the radiolabeled drug with human neuroblastoma cells (SK-N-SH) that overexpress the β .III-tubulin, an isoform where Cys239 is replaced by a serine residue. The results clearly showed that β .III-tubulin is not alkylated by [urea-14C]-4-tBCEU, suggesting that cysteine 239 residue is essential for the reactivity of 4-tBCEU with β -tubulin. Taken together, these findings indicate that the mechanism of cytotoxicity of CEU involves microtubule depolymn. through alkylation of β -tubulin.

IT 102433-48-7 113849-19-7 118202-59-8
161194-45-2 161194-47-4

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(microtubule disruption induced by β -tubulin alkylation by 1-aryl-3-(2-chloroethyl)ureas, novel class of soft alkylating agents)

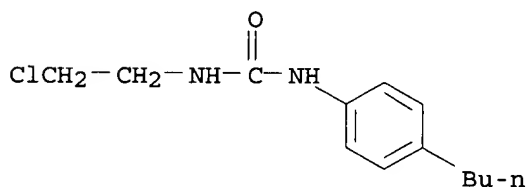
RN 102433-48-7 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-(4-ethylphenyl)- (9CI) (CA INDEX NAME)



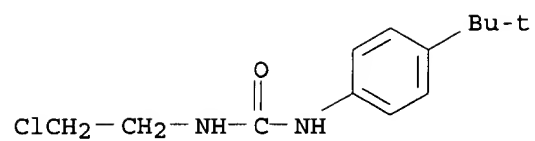
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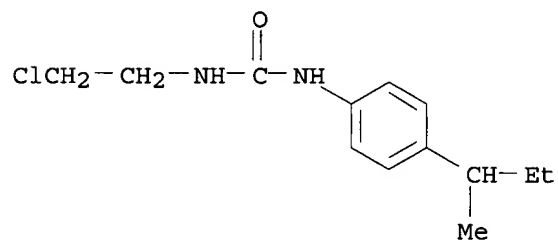
RN 118202-59-8 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-45-2 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CAPLUS

CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)

